RECENT PROGRESS IN ASYMMETRIC SYNTHESIS OF PYRROLIZIDINES†

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Abstract----Asymmetric syntheses of optically active pyrrolizidines are reviewed according to the chiral pools used.

CONTENTS

1. INTRODUCTION

The pyrrolizidines[1] are called as necine bases, which have in common the azabicyclo[3.3.0]octane ring system, as illustrated in Figure 1. These bases are variously functionalized on the parent skeleton and are present as mono-ols, diols, and triols. The bases themselves have been isolated from natural sources, but more often they are found as esters (*e.g.*, 1), diesters, or macrocyclic bislactones (*e.g.*, 2). Various members of this family exhibit remarkably diverse types of biological activity.[2] The pyrrolizidine alkaloids have been known to have antitumor, hypotensive, local anesthetic, antispasmodic, antiinflammatory, carcinogenic, or hepatotoxic activity. The double bond on the pyrrolizidine skeleton seems to be essential for the biological activities. For example, indicine *N*-oxide 1, a monoester of (+)-retronecine, has been used as antitumor agent in clinical trials.[2e] Since the first synthesis of retronecine in racemic form by Geissman and Waiss in 1962,[4] total synthesis of pyrrolizidine alkaloids has been

† Dedicated to the memory of Professor Tetsuji Kametani.

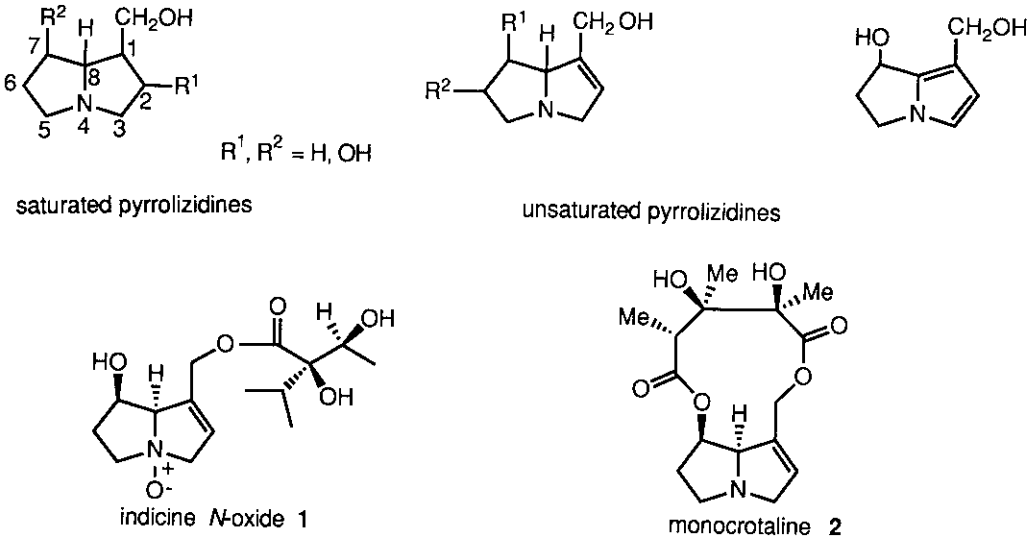


Figure 1

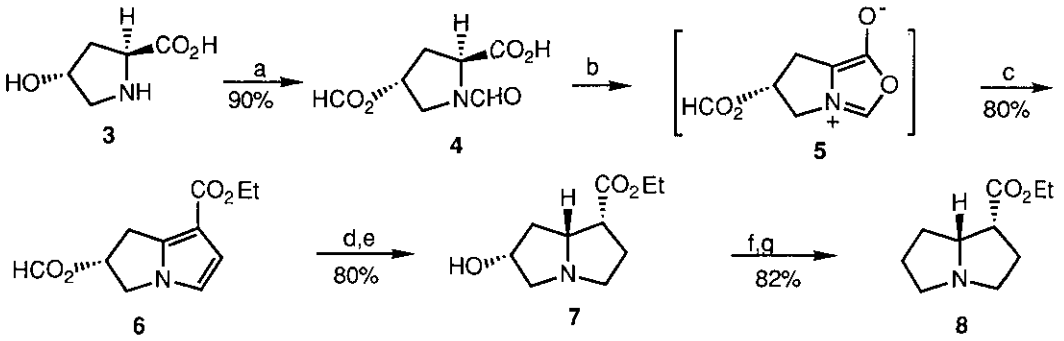
an attractive subject for synthetic organic chemists, because of their unique structures and intriguing biological activity. A number of new synthetic routes to racemic pyrrolizidines have been reported,[1j] but the synthesis of optically active compounds appeared recently since the first asymmetric synthesis of pyrrolizidines by Robins and Sakdarat in 1979.[4] During the passed dacade, a lot of enantioselective syntheses of pyrrolizidine alkaloids have been reported, in which chiral building blocks derived from *L*-proline derivatives, malic acids, or carbohydrates were commonly used. This article reviews the literature from 1979 to the end of 1988 on asymmetric syntheses of pyrrolizidines. The authors' recent work on the asymmetric synthesis of pyrrolizidine alkaloids employing chiral tin(II) enolates was also included in the last part of this article.

2. UTILIZATION OF *L*-PROLINE DERIVATIVES

The naturally occurring *L*-proline and 4-hydroxy-*L*-proline possess the half part of the pyrrolizidine ring system with the correct absolute stereochemistry at the C(8) center. For pyrrolizidine synthesis, the remaining problem is how to construct another half part of the molecule with retention of the chirality at the initial C(8) center and induction of a new chiral center at C(1) position of the bicyclic skeleton.

The first chiral synthesis of optically active pyrrolizidines was reported by Robins and Sakdarat as mentioned above.[4,5] A regioselective 1,3-dipolar cycloaddition of ethyl propiolate to the postulated azomethine ylide 5[6] derived from the *NO*-diformyl derivative 4 of natural (-)-4-hydroxy-*L*-proline 3 with formic acid in the presence of acetic anhydride was employed as a key reaction to construct the pyrrolizidine nucleus. The bicyclic compound 6 was prepared via this

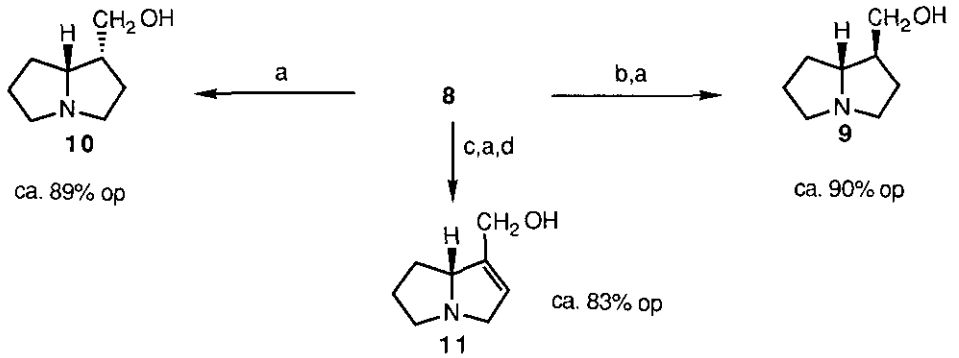
Scheme I [a]



[a] (a) HCO_2H, Ac_2O; (b) Ac_2O; (c) $HC{\equiv}CCO_2Et$; (d) NH_3, EtOH; (e) H_2, 10% Pd/C, AcOH;(f) $SOCl_2$; (g) H_2, Raney Ni.

reaction in 80% yield from 4 (Scheme I). The 4-hydroxy group on the initial proline moiety was used to control the stereochemistry of the two newly formed chiral centers at C(1) and C(8) during catalytic hydrogenation of 6. The hydroxy compound 7 was obtained from 6 stereoselectively and then the hydroxy group in 7 was removed from the nucleus by displacement with chlorine, followed by catalytic hydrogenation to afford the ester 8. Reduction of 8 with lithium aluminum hydride gave (+)-isoretronecanol 10 in 45% overall yield from 3. The thermodynamically less stable endo-ester 8 was epimerized at C(1)[7] to produce the corresponding exo-ester which was reduced to (+)-laburnine (or (+)-trachelanthamidine) 9 in 31% overall yield from 3. The ester 8 was also converted to (+)-supinidine 11 through the known procedures for the racemic one[8] (Scheme II). The other three 8α-pyrrolizidines 15, 16, and 17 were similarly synthesized from 13, the enantiomer of 6, as shown in Scheme III. This work provides a general synthetic route to all six naturally occurring 1-hydroxymethylpyrrolizidines starting from (-)-4-hydroxy-*L*-proline 3 with optical purity better than 80% in every case.

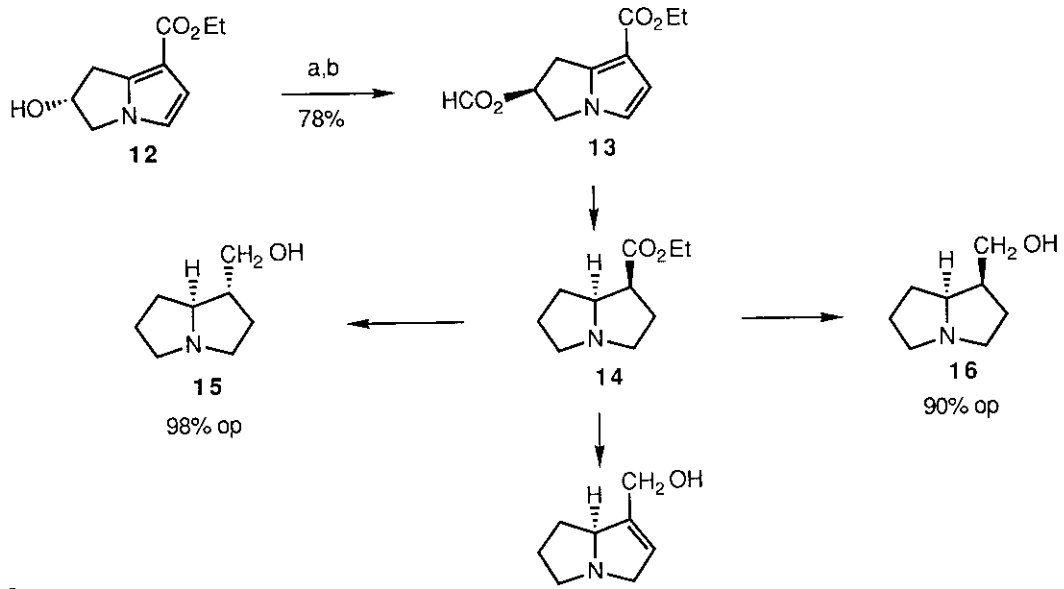
Scheme II [a]



[a] (a) $LiAlH_4$; (b) NaOEt/EtOH; (c) *i*-Pr_2NH/*n*-BuLi, PhSeCl; (d) H_2O_2.

A Dieckmann cyclization of the chiral diester 19[9] was adopted by Rüeger and Benn in their synthesis of 1-hydroxymethylpyrrolizidines (Scheme IV). Two

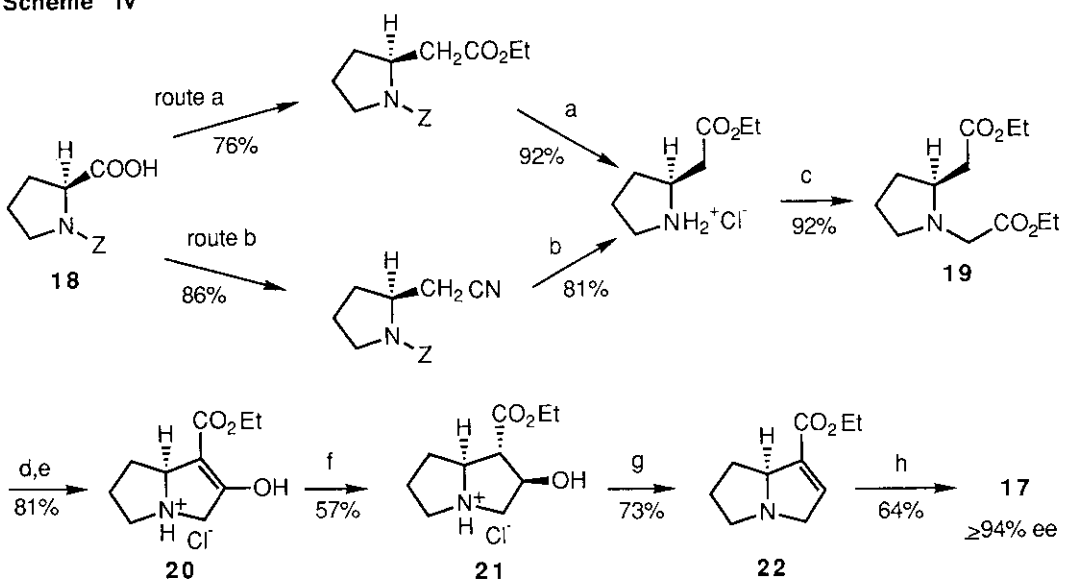
Scheme III [a]



[a] (a) TsCl/Py; (b) $Et_4N^+CHO^-_2$.

homologation methods were used to prepare the chiral diester 19 from *L*-proline. Dieckmann cyclization of the diester 19 was achieved under the equilibrium control conditions[10] to afford the desired pyrrolizidine keto ester 20 in the enol form. The sodium cyanoborohydride reduction of the keto ester 20 proceeded

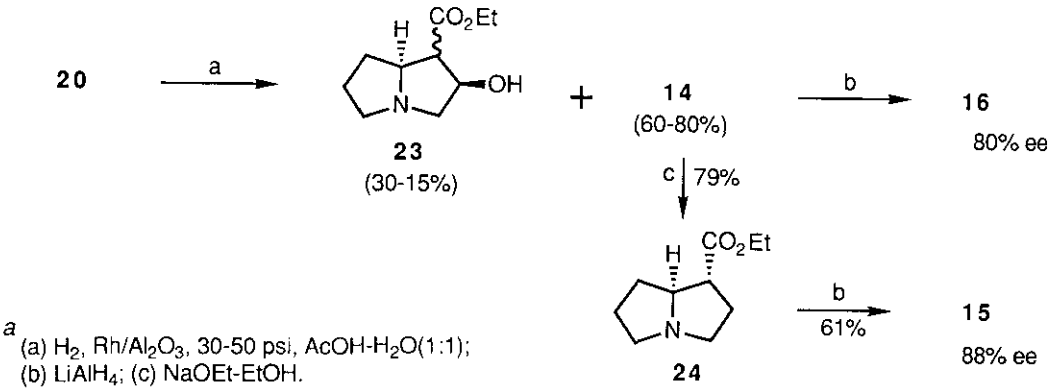
Scheme IV [a]



[a] route a: $(COCl)_2$, DMF(cat); CH_2N_2; Ag_2O, EtOH; route b: BH_3·SMe_2; TsCl/Py;NaCN, DMSO; (a) Pd/C, H_2; (b) HCl, EtOH; H_2O; HCl, EtOH; (c) $BrCH_2CO_2Et$,Na_2CO_3; (d) NaOEt; (e) AcOH, H_2O; (f) $NaBH_3CN$, H_2O; (g) MsCl/Et_3N; (h) Dibal.

stereoselectively to give the hydroxy ester 21, which was converted into (-)-supinidine 17 according to the method of Tufariello and Lee[11] for the racemic compound. On the other hand, the catalytic hydrogenation of the keto ester 20 gave a mixture of 14 and 23, separable by column chromatography. The ester 14 was converted to (-)-isoretronecanol 16 and (-)-trachelanthamidine 15 (Scheme V).

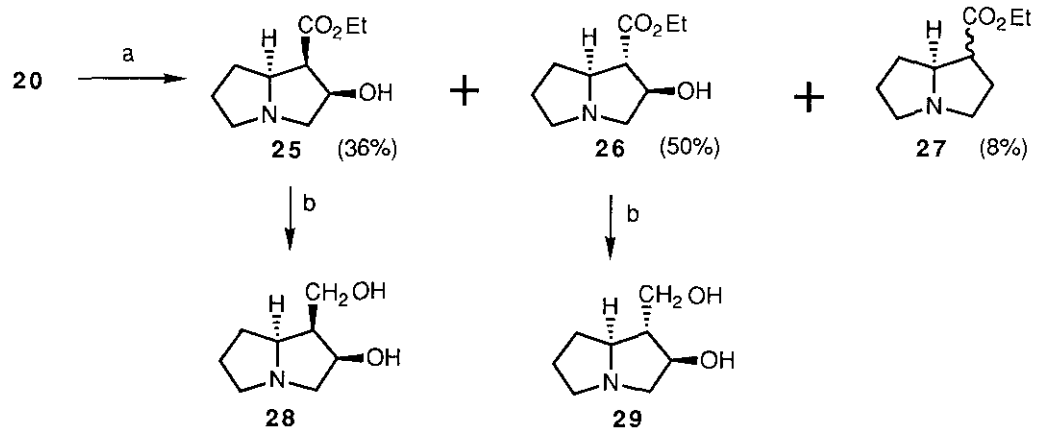
Scheme V [a]



[a] (a) H_2, Rh/Al_2O_3, 30-50 psi, AcOH-H_2O(1:1); (b) $LiAlH_4$; (c) NaOEt-EtOH.

The keto ester 20 was also used to synthesize 2-hydroxylated necines by Rüeger and Benn[12] as shown in Scheme VI. Hydrogenation of 20 over platinum black gave 25 and 26 in 36% and 50% yields, respectively, together with a diastereomeric mixture 27 (8%). Reduction of esters 25 and 26 with lithium aluminum hydride gave (-)-petasinecine 28 and its epimer 29, respectively.

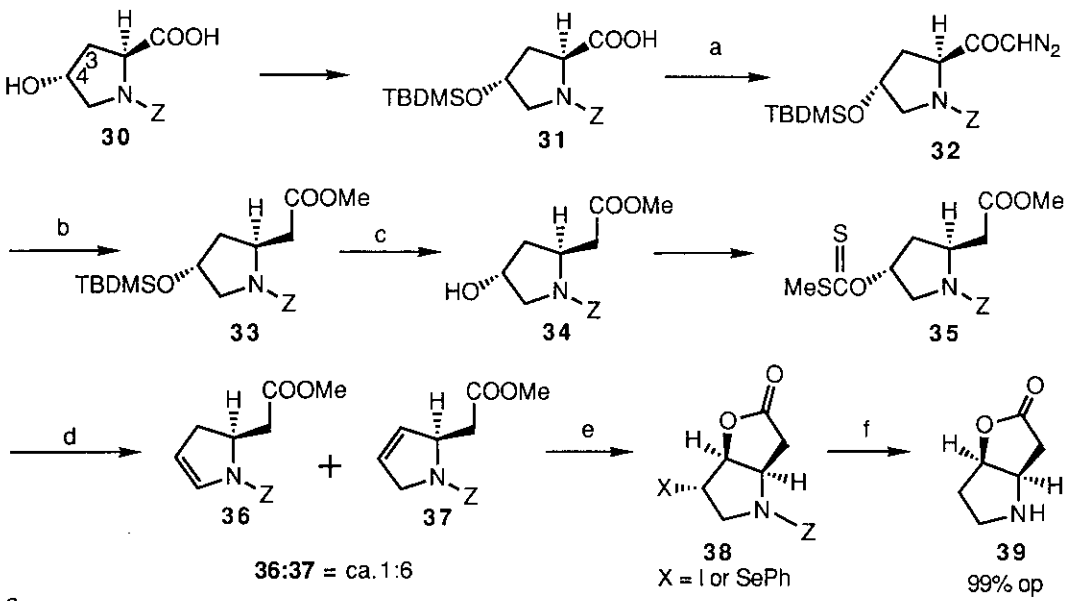
Scheme VI [a]



[a] (a) H_2/Pt, AcOH-H_2O(1:1), 40-50 psi, 0 °C; aq.K_2CO_3; (b) $LiAlH_4$.

(-)-4-Hydroxy-*L*-proline derivative 30 was also used by Benn and co-workers in their synthesis of more complex necine bases.[13] The optically active Geissman-Waiss lactone 39[3] was prepared from 30 via homologation of the carboxylic group and transposition of the hydroxy group from C(4) to C(3) with inversion of configuration (Scheme VII).[13a] The homologation was successful via Wolff rearrangement of the diazoketone 32. Elimination of the C(4) hydroxy group was manipu-

Scheme VII[a]



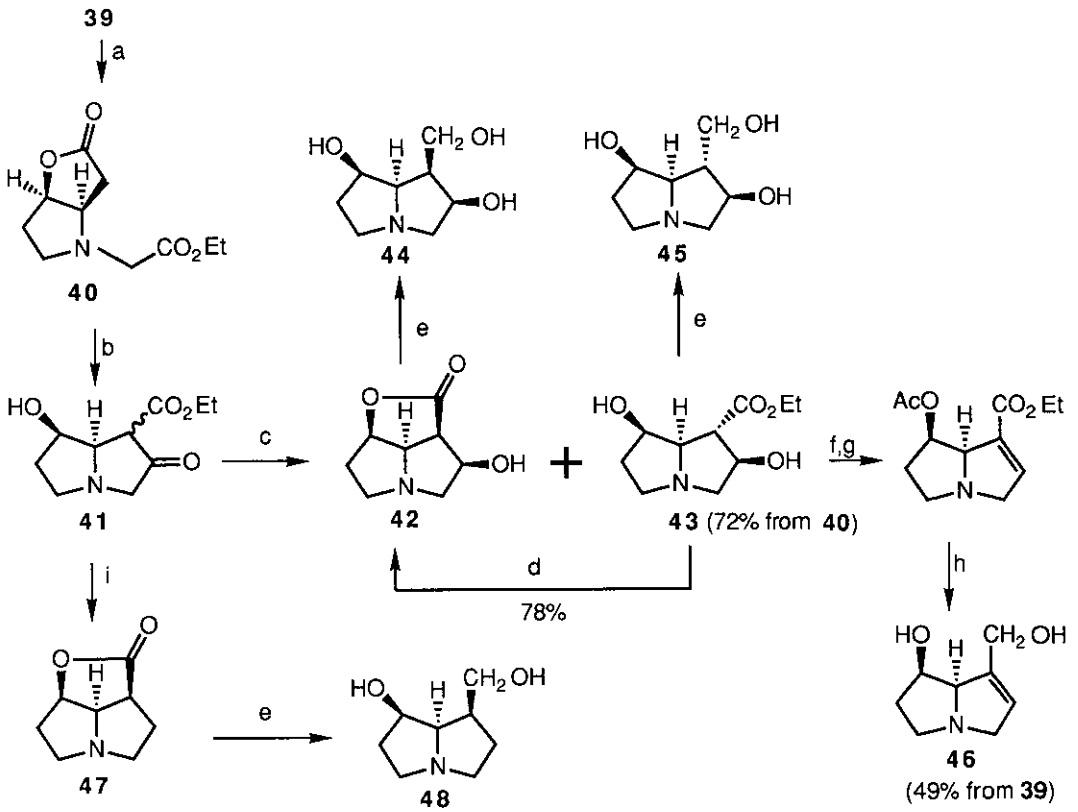
[a](a) isobutyl chloroformate, Et_3N; CH_2N_2; (b) Ag_2O, MeOH; (c) n-$Bu_4N^+F^-$, THF; (d) pyrolysis; (e) MeOH-H_2O, Na_2CO_3; I_2-KI-$NaHCO_3$ or PhSeCl; (f) n-Bu_3SnH;5% Pd/C, EtOH, HCl.

lated via the xanthate 35, as described by Dormoy's group,[14] to afford the desired olefin 37 predominantly (36:37 = ca. 1:6). Electrophilic lactonization of the carboxylic acid derived from 37 followed by reductive removal of I or PhSe group from 38 gave the Geissman-Waiss lactone 39. The enantiomeric purity of 39 was determined to be at least 99% by Mosher's procedure.[15]

Conversion of 39 to (+)-retronecine 46 was done by the modification of the Geissman-Waiss[3] and Narasaka[16] methods as shown in Scheme VIII.[13b] Dieckmann condensation of 40 in the presence of potassium ethoxide in toluene at room temperature was proved to be the best for the conversion of 40 to the keto ester 41, which was reduced, without purification, to the dihydroxy ester 43 in 72% yield, accompanied by minor amount of the hydroxy lactone 42. Reduction of 42 and 43 with lithium aluminum hydride gave the triols 44 and 45, respectively. The dihydroxy ester 43 was converted to (+)-retronecine 46 in 49% overall yield from 39. On the other hand, hydrogenation of 41 using rhodium on alumina catalyst afforded mainly the lactone 47. Reduction of 47 with lithium aluminum hydride gave (-)-platynecine 48. Thus, this work presents the first enantioselective synthesis of (+)-croalbinecine 45, (+)-retronecine 46, and (-)-platynecine 48.

Benn and co-workers[13c] have developed an alternative route from 30 to the triol, (+)-crotanecine 54 (Scheme IX). Thus, 30 was converted to the olefinic nitrile 49 with high regioselectivity in the double bond formation step.[17] Treatment of 49 with *N*-iodosuccinimide in acetic acid gave an iodo compound, which on treatment with acetic acid and silver acetate afforded a mixture. It was hydrolized to give the hydroxy lactones 50 and 51 in a 95:5 ratio. Further treat-

Scheme VIII[a]



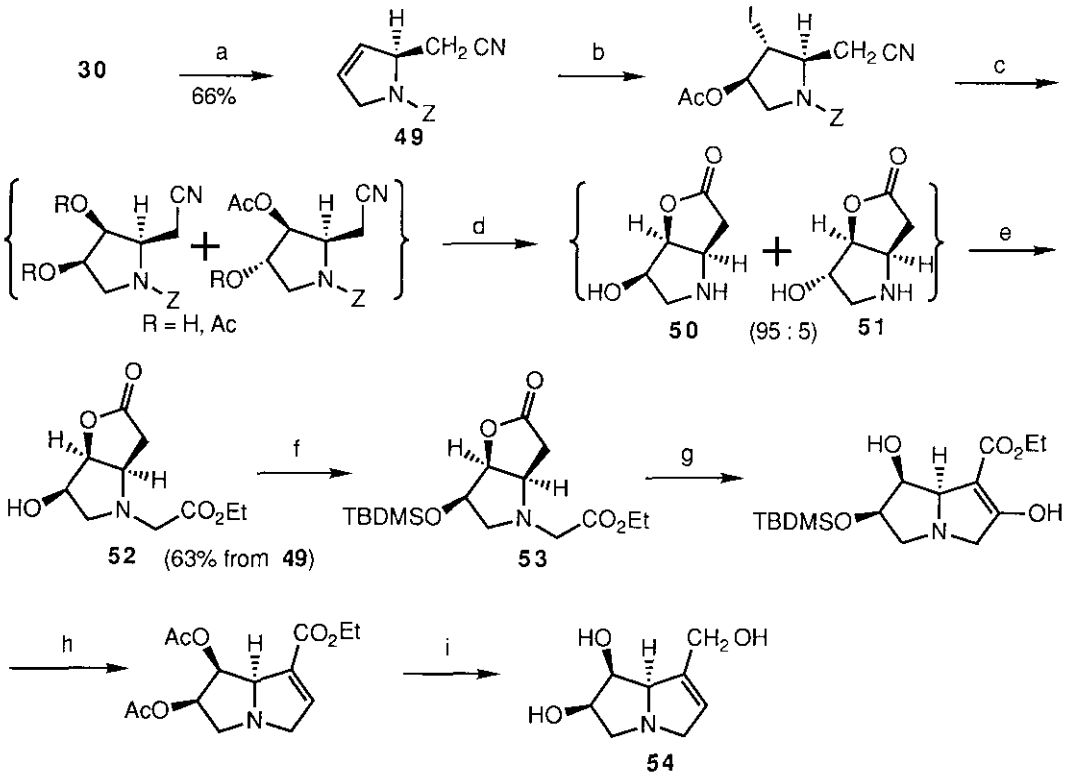
[a] (a) $BrCH_2CO_2Et$; (b) KOEt-PhMe , rt, 4 h; (c) H_2/PtO_2, AcOH-H_2O (1:1); (d) NaOEt (cat),EtOH, rt, 30 days; (e) $LiAlH_4$; (f) Ac_2O/Py, DMAP; (g) NaH, THF; (h) EtOH-HCl; $LiAlH_4$;(i) H_2, Rh/Al_2O_3, AcOH-H_2O (1:1).

ment of 50 and 51 with ethyl bromoacetate yielded the desired compound 52 in 63% overall yield from 49. The compound 52 was transformed to (+)-crotanecine 54, through the procedure described for the (+)-retronecine synthesis, in 4% overall yield from 30. This work presents the first enantioselective synthesis of this pyrrolizidine triol.

A cationic olefin cyclization of a Pummerer reaction intermediate[18] was developed in the synthesis of optically active (-)-trachelanthamidine 15 from *L*-prolinol 55 by Ikeda's group.[19] When the sulfoxide 57 prepared from *L*-prolinol 55 was treated with a stoichiometric amount of trifluoroacetic anhydride, cyclization of the corresponding Pummerer reaction intermediate 58 was accomplished to give the bicyclic product 60 via 59 (Scheme X). The stereochemical outcome of this cyclization was interpreted according to the stereoelectronic[20] and steric preferences of the reaction. The cyclization product 60, a mixture of ca. 4:1 of C(2) stereoisomers, was converted to (-)-trachelanthamidine 15 via 61.

An orthoester Claisen rearrangement of an intermediate 64 derived from *L*-proline derivative 62 has been used in the synthesis of (-)-isoretronecanol 16 and

Scheme IX [a]

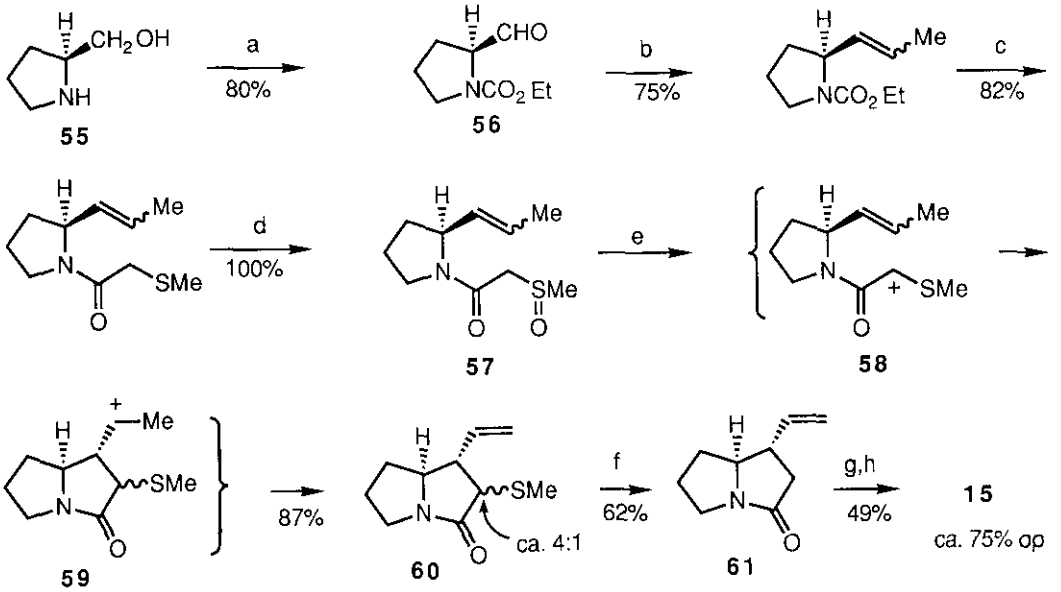


[a] (a) $BH_3 \cdot SMe_2$, THF, 0 °C; TsCl/Py, 0 °C; NaCN, DMF, 95 °C; PhSeNa, THF-MeOH, 65 °C; H_2O_2, 5 °C; Δ (rt); (b) NIS, AcOH, 60 °C; (c) AcOH-H_2O (4:1)-AgOAc, 95 °C; (d) MeOH-HCl, rt; (e) $BrCH_2CO_2Et$, Na_2CO_3, EtOH, 75 °C; column chromatography; (f) TBDMSCl, imidazole, 55 °C; (g) KOEt, PhMe , 0 °C to rt; (h) $NaBH_3CN$, H_2O, pH 4,rt; Ac_2O, DMF, 65 °C; *n*-$Bu_4N^+F^-$, THF, rt; Ac_2O, rt; (i) Dibal, THF, -78 °C to rt.

(-)-trachelanthamidine 15 by Saito and co-workers.[21] The γ-amino-α,β-unsaturated ester 63 prepared from *N*-Boc-*L*-proline methyl ester 62 was reduced with Dibal in the presence of $BF_3 \cdot OEt_2$[22] to give 64 in 83% yield. Orthoester Claisen rearrangement of 64 afforded a mixture of the diastereomeric esters 65 (H_a, α:β = 2.6:1). The formation of the major product was explained according to the chair-like six-membered cyclic transition state 69. The mixture of 65 was subjected to ruthenium-catalyzed oxidation[23] followed by esterification to yield 66. Deprotection of the amino group and intramolecular amidation promoted by $AlMe_3$[24] gave the pyrrolizidinone compounds 67 and 68 in a diastereomeric ratio of 2.7:1. This ratio was changed to 1:4.4 (67:68) by treatment with sodium methoxide in methanol. Reduction of the esters 67 and 68 with $LiAlH_4$ yielded (-)-isoretronecanol 16 and (-)-trachelanthamidine 15, respectively.

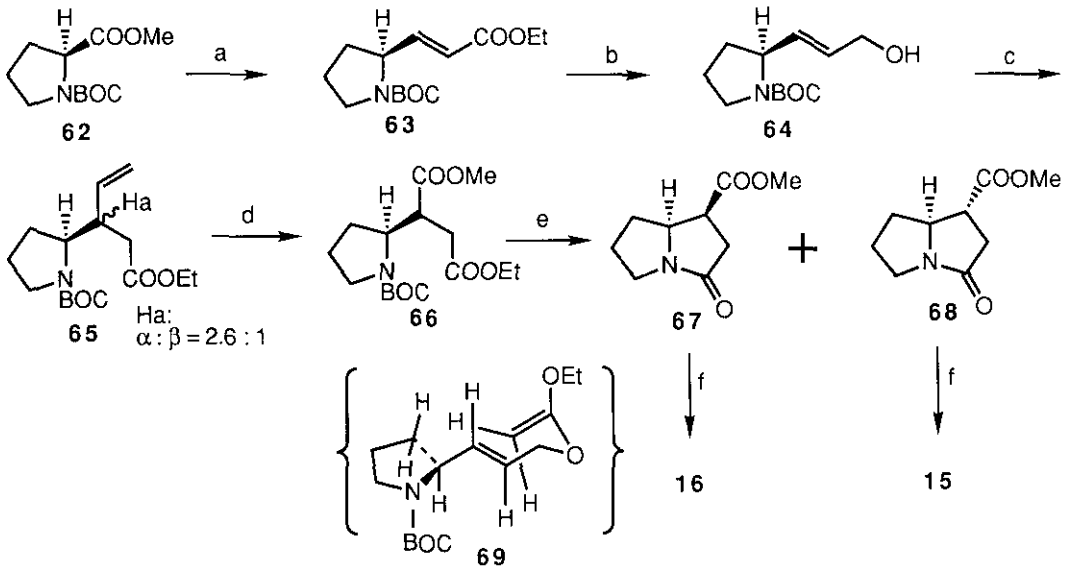
An enantioselective synthesis of (-)-trachelanthamidine 15 from *L*-proline derivative 70 was reported by Jolly and Livinghouse,[25] in which an atom-transfer

Scheme X [a]



[a] (a) $ClCO_2Et$, 4 *M* NaOH; DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2, -60 °C; (b) $Ph_3P^+EtBr^-$, $NaCH_2SOMe$, DMSO, THF; (c) NaOH, $HOCH_2CH_2OH$-H_2O (5:1), reflux; $MeSCH_2COCl$, Et_3N, Et_2O; (d) $NaIO_4$, MeOH-H_2O (1:1); (e) $(CF_3CO)_2O$, CH_2Cl_2; (f) $NaIO_4$, MeOH-H_2O (1:1); Al(Hg), 2.5% aq THF; (g) OsO_4 (cat), $NaIO_4$, THF-H_2O (4:1); (h) $LiAlH_4$, THF, reflux.

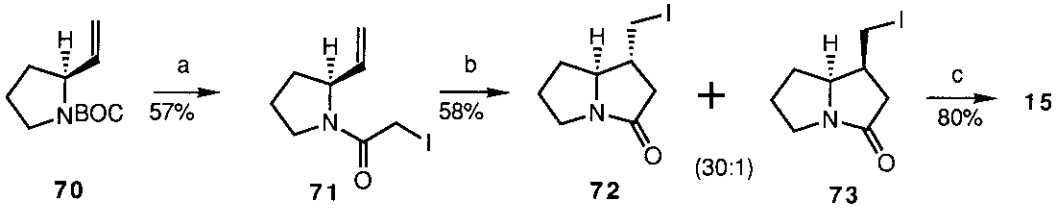
Scheme XI [a]



[a] (a) Dibal; $(i\text{-}PrO)_2POCHCO_2EtNa^+$; (b) Dibal, $BF_3{\cdot}OEt_2$; (c) $MeC(OEt)_3$, H^+, 140 °C; (d) $RuCl_3$, $NaIO_4$; CH_2N_2; (e) CF_3CO_2H; $AlMe_3$; (f) $LiAlH_4$.

γ-lactamization was developed. The required allylic α-iodoacetamide 71 was prepared from (*S*)-2-vinyl-*N*-(tert-butoxycarbonyl)pyrrolidine 70 in 57% overall yield. Cyclization of the iodoacetamide 71 was executed with $(Bu_3Sn)_2$ (0.55 equiv.) in the presence of EtI (3.5 equiv., PhH, sunlamp) to furnish the pyrrolizidinones 72 and 73 (30:1) in 58% yield. This result provided the first example of diastereoface selection in an atom-transfer annulation. Treatment of the mixture with CsO_2CEt followed by reduction afforded (-)-trachelanthamidine 15 in 80% yield.

Scheme XII [a]



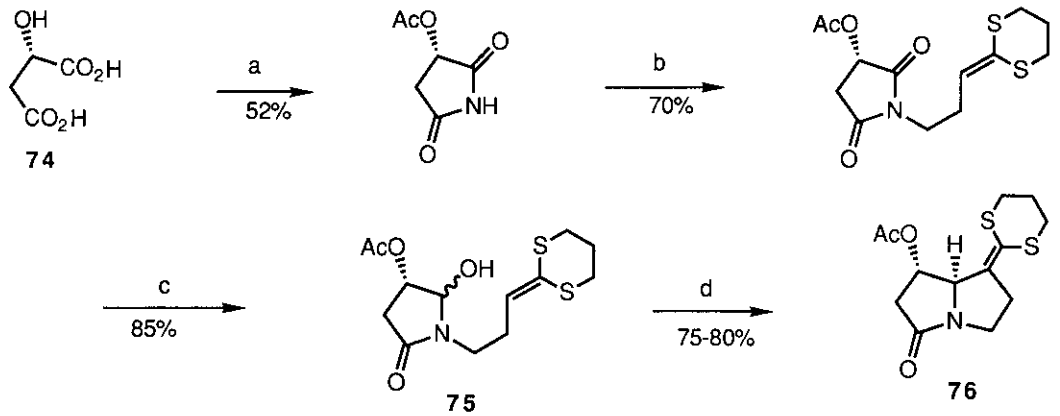
[a] (a) CF_3CO_2H; $(ClCH_2CO)_2O$, R_3N; NaI, MeCN; (b) $(Bu_3Sn)_2$ (0.55 eq.),EtI (3.5 eq.), *hv*; (c) CsO_2CEt, DMF; $LiAlH_4$.

3. UTILIZATION OF (*S*)- AND (*R*)-MALIC ACIDS

Unsaturated pyrrolizidine diols commonly have a chiral hydroxy group at the C(7) center. Malic acids have attracted a lot of attention in the asymmetric syntheses of these pyrrolizidine diols because malic acids could be gotten in any enantiomeric pure form and also the chiral hydroxy group in the malic acids could be used to control the stereochemistry of C(8) center during C-C bond formation reaction at that position. Intramolecular cationic and radical cyclizations have been shown to be excellent for the construction of C(8)-C(1) bond with almost complete induction of chirality from C(7) to C(8).

Chamberlin and Chung[26] have reported a general synthetic route to seven pyrrolizidine diols from a single precursor 76, which was prepared from (*S*)-malic acid 74 via the key step of an intramolecular acyliminium ion-ketene dithioacetal cationic cyclization of 75 (Scheme XIII). The acetoxy group in 75 is proved to be very efficient to block the α-face of the acyliminium ion, resulting in very highly asymmetric induction during the cyclization step. Only ca. 3% of the bridgehead diastereomer of 76 was detected. Another advantage of this route is in the fact that the ketene dithioactal substituent in 75 serves as an efficient cationic cyclization terminator and for introducing a double bond to the C(1)-C(2) position via a regioselective double bond migration in later steps (Scheme XIV). Starting from 76, four 7(*S*) diols 77, 78, 79, and 81 were synthesized in 8-11% overall yields from (*S*)-malic acid 74. For the synthesis of 7(*R*) diols, Chamberlin and Chung adopted an oxidation-reduction procedure for the conversion of 7(*S*)- to 7(*R*)-configuration. Since the attempted Swern oxidation of 80 to the corresponding ketone resulted in the racemization at the bridgehead carbon due

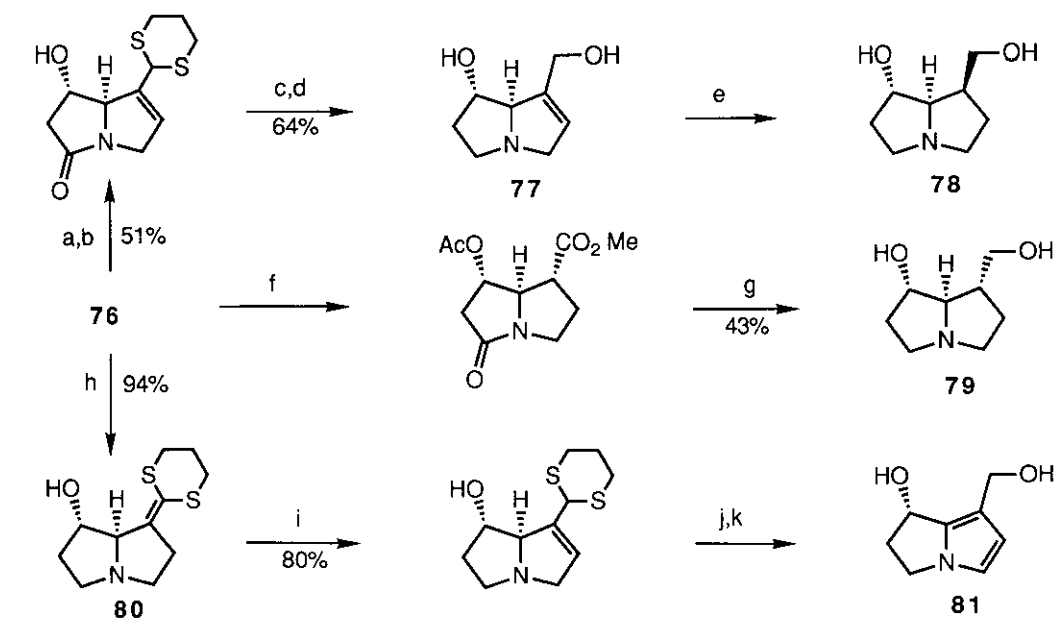
Scheme XIII [a]



[a] (a) AcCl; NH_3; AcCl; (b) 2-(3-hydroxypropylidene)-1,3-dithiane, Ph_3P, EtO_2CNNCO_2Et; (c) $NaBH_4$, MeOH, -4 °C; (d) $MeSO_2Cl$, Et_3N, CH_2Cl_2, -20 to 20 °C.

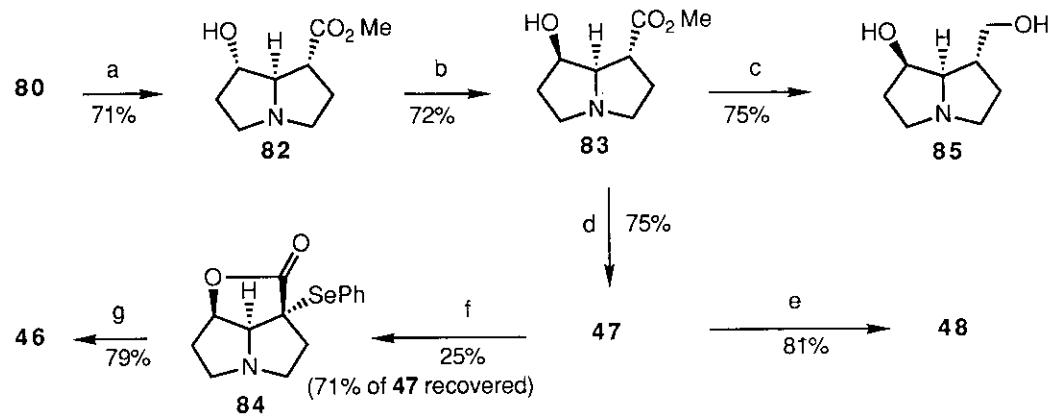
to the presence of the ketene dithioacetal substituent, 80 was converted to the methyl ester 82, which was then submitted to Swern oxidation and hydrogenation to give the 7(*R*) epimer 83 (Scheme XV). Thus, three 7(*R*) diols 85, 48, and 46 were prepared in ca. 2-9% overall yields from (*S*)-malic acid. The difficulty in the deprotonation of the tricyclic lactone 47 to form the corresponding enolate resulted in the low yield of the phenylselenylation product 84. Seventy one per-

Scheme XIV [a]



[a] (a) MeONa; (b) LDA, MeOH; (c) $HgCl_2$, MeCN-H_2O, $CaCO_3$; (d) $LiAlH_4$; (e) H_2, Raney Ni; (f) HCl-MeOH, $HgCl_2$; (g) $LiAlH_4$; (h) AlH_3; (i) LDA, MeOH; (j) $HgCl_2$, MeCN-H_2O, $CaCO_3$; (k) $NaBH_4$.

Scheme XV [a]

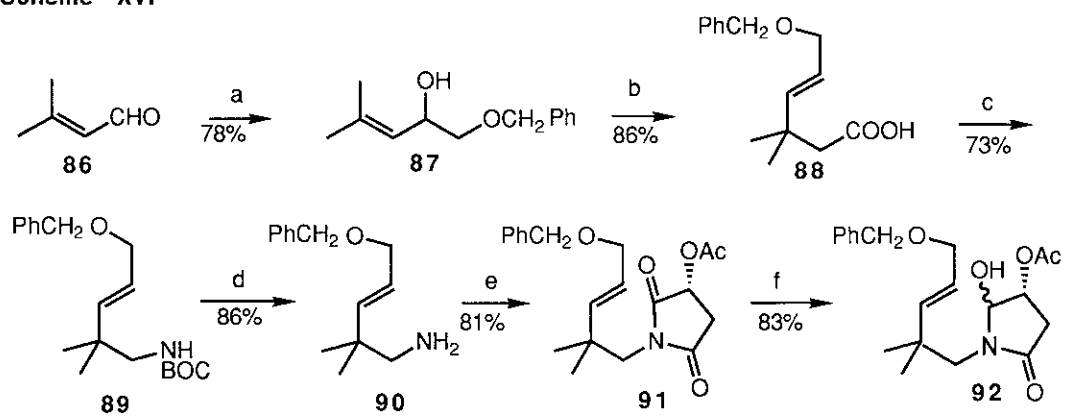


[a] (a) $HgCl_2$, HCl-MeOH, CF_3CO_2H; (b) Swern oxidation; H_2/PtO_2, 20 °C, 4 h; (c) $LiAlH_4$; (d) NaOEt-EtOH, reflux; (e) $LiAlH_4$; (f) LDA, $PhSe_2Ph$; (g) $LiAlH_4$; H_2O_2, HOAc.

cent of the starting material 47 was recovered in this reaction, which was used for recycling.

The first enantioselective approach to dihydroxypyrrolizidine was reported by Hart and Yang[27] in 1983. The key step is an *N*-acyliminium ion rearrangement-cyclization process, which was enantioselectively controlled by a chiral acetoxy group in the *N*-acyliminium ion precursor 92 (Scheme XVI). The carboxylic acid 88 was prepared from 87 via Johnson orthoester Claisen rearrangement followed by saponification. Curtius degradation of the acid chloride of 88 gave 89 which afforded the amine 90 upon treatment with trifluoroacetic acid. Coupling of 90 with (*R*)-2-acetoxysuccinic anhydride gave the imide 91 which was reduced with sodium borohydride to yield the hydroxy lactam 92. The stereoselective conversion of 92 to 94a, b in the presence of formic acid was rationalized by considering that the initial rearrangement proceeded via a transition state 93 having a

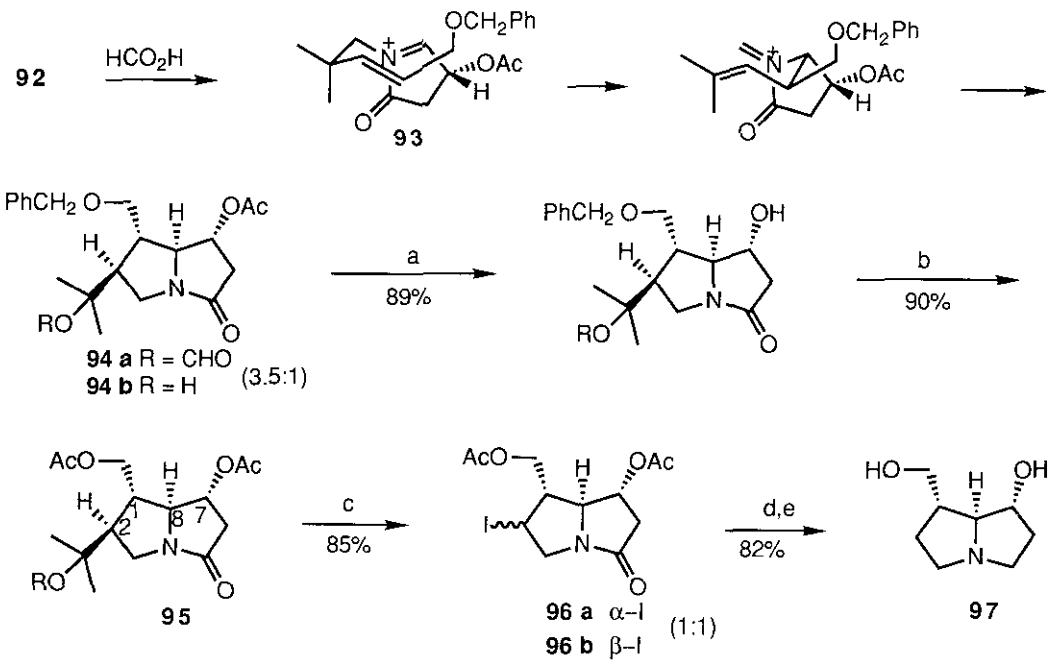
Scheme XVI [a]



[a] (a) $PhCH_2OCH_2Li$; (b) triethyl orthoacetate/propanoic acid, Δ; 10% NaOH; (c)$SOCl_2$; NaN_3; PhH, reflux; ^{t}BuOK/^{t}BuOH; (d) CF_3CO_2H; (e) (*R*)-2-acetoxysuccinic anhydride; AcCl; (f) $NaBH_4$, MeOH.

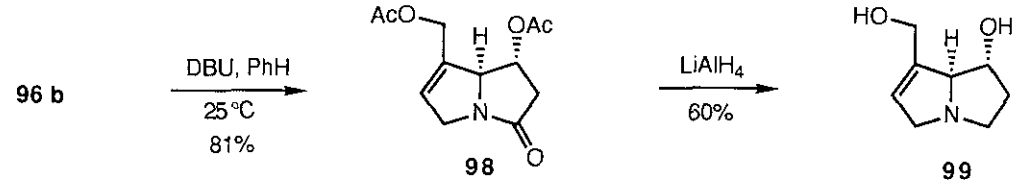
minimal steric interaction between the benzyloxymethyl and acetoxy groups (Scheme XVII). The degradation of the C(2) side chain in 95 was successful via alkoxy radical fragmentation,[27a] which gave a mixture of 96a and 96b in 85% yield together with 98 (6%). Finally, (-)-hastanecine 97 was derived from 96; 16% overall yield of the alkaloid was reported from 86. The synthesis of (-)-heliotridine 99 from 96b was shown in Scheme XVIII.

Scheme XVII [a]



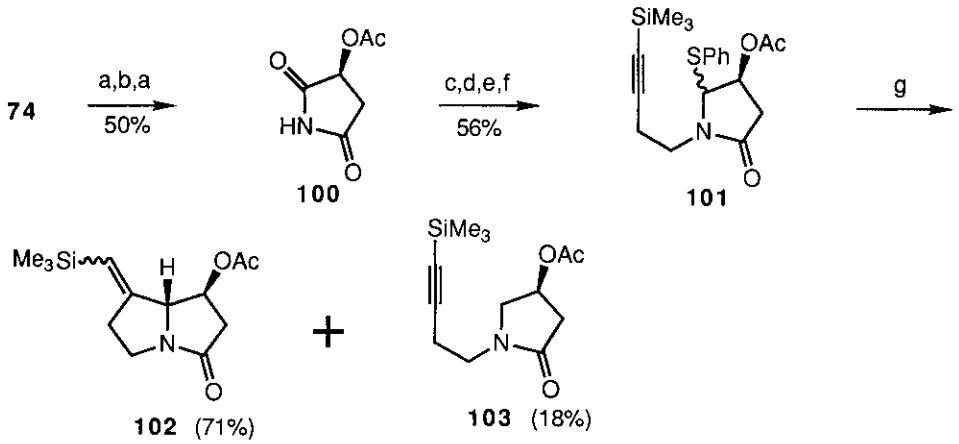
[a] (a) NaOH, MeOH; (b) H_2, Pd/C, EtOH; Ac_2O/Py; (c) HgO, I_2, CCl_4; (d) n-Bu_3SnH,AIBN; (e) $LiAlH_4$.

Scheme XVIII



Choi and Hart[28] have reported another similar synthetic route to three 7(*S*) pyrrolizidines from (*S*)-malic acid 74. The construction of the C(1)-C(8) bond is based on the key reaction of an intramolecular addition of α-acylamino radicals to alkynes.[29] The chiral α-acylamino radical precursor 101 was obtained from (*S*)-malic acid 74 as shown in Scheme XIX. Treatment of 101 with n-Bu_3SnH and AIBN in benzene gave a mixture of the geometrical isomers 102 in 71% yield together with the reduction product 103 (18%). The use of a terminal trimethylsilyl substituent in acetylene 101 gave the merit that the cyclization provided the exo-products exclusively due to the steric effects.[28] Similarly to other

Scheme XIX [a]

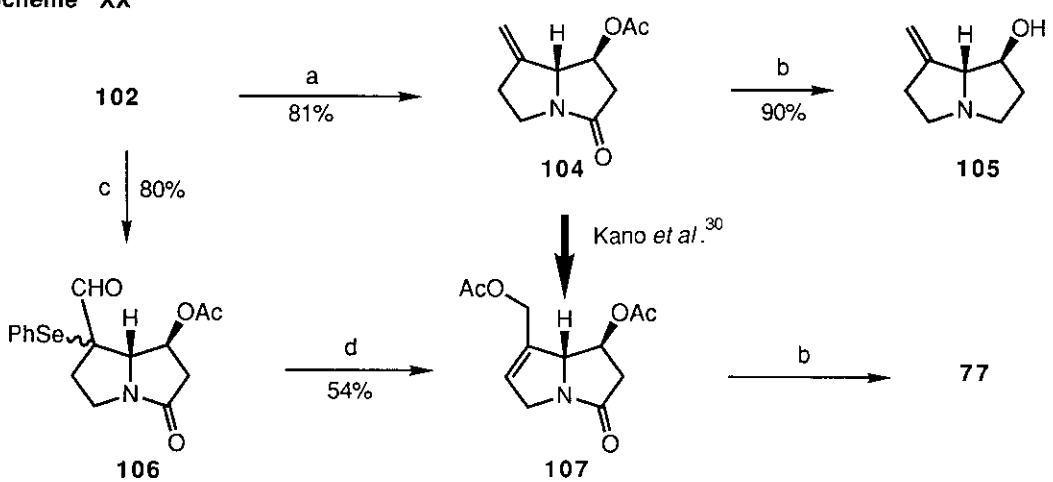


[a] (a) AcCl; (b) NH_3; (c) Ph_3P, EtO_2CNNCO_2Et, $Me_3SiC{\equiv}CCH_2CH_2OH$; (d) $NaBH_4$; (e) Ac_2O, Et_3N, DMAP; (f) PhSH, TsOH; (g) *n*-Bu_3SnH, AIBN, 80 °C, PhH.

cases,[26b,27b] the chiral acetoxy group in 101 efficiently controls the stereochemistry of the intramolecular process. The cyclization proceeded with excellent diastereoselectivity at C(8); only 3–5% of the diastereomer at that center was isolated. The mixture 102 was converted to (-)-dehydrohastanecine 105, (+)-heliotridine 77, and (+)-hastanecine 79 as shown in Schemes XX and XXI.

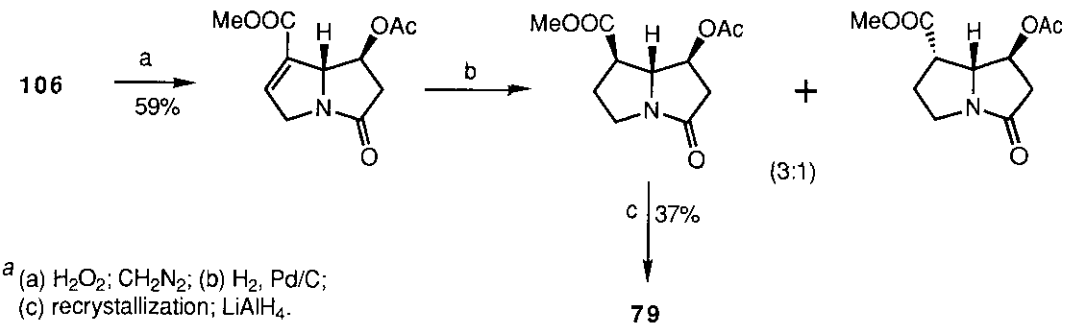
An alternative synthesis of (+)-heliotridine 77 from an intermediate 104 was reported by Kano and co-workers.[30] Compound 104 was converted to 107 in 68% yield by the following procedures: hydrolysis of the acetate (K_2CO_3, MeOH), conversion of exo-methylene group to allylic alcohol (CF_3CO_2Ag, PhSeCl, THF; Na_2CO_3, MeOH; 30% H_2O_2), and acetylation (Ac_2O, Et_3N, DMAP).

Scheme XX [a]



[a] (a) $PhSO_2H$, MeCN-H_2O; (b) $LiAlH_4$; (c) MCPBA; HCO_2H, H_2O; $PhSeNEt_2$;(d) $NaBH_4$; Ac_2O, Et_3N, DMAP; H_2O_2.

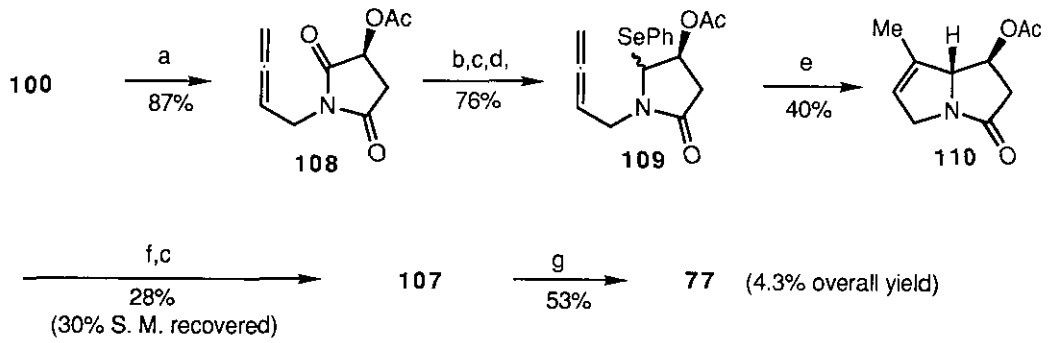
Scheme XXI [a]



[a] (a) H_2O_2; CH_2N_2; (b) H_2, Pd/C; (c) recrystallization; $LiAlH_4$.

An allene moiety has been used for free radical cyclization in the asymmetric synthesis of (+)-heliotridine 77 and (-)-dihydroxyheliotridane 78 from (*S*)-malic acid.[31] The free radical precursor 109 was prepared from the chiral imide 100 by Mitsunobu coupling, reduction, Steglich acetylation, and displacement of the acetoxy group by phenylseleno function (Scheme XXII). The selenide 109 was treated with *n*-Bu_3SnH and AIBN in benzene under reflux to furnish the major product 110 in 40% yield together with other three minor products (bridgehead and double bond isomers). The major product 110 was formed by attack of the allene on the radical face opposite to the acetoxy group and exocyclic reduction of the resulting allylic radical. The diastereoselectivity at the bridgehead carbon is ca. 40:17, which is less selective than in the cyclization involved with attack of α-acylamino radical at an sp-hybrid carbon (see Scheme XIX).[28] The product was converted to (+)-heliotridine 77 in a 4.3% overall yield from the chiral imide 100.

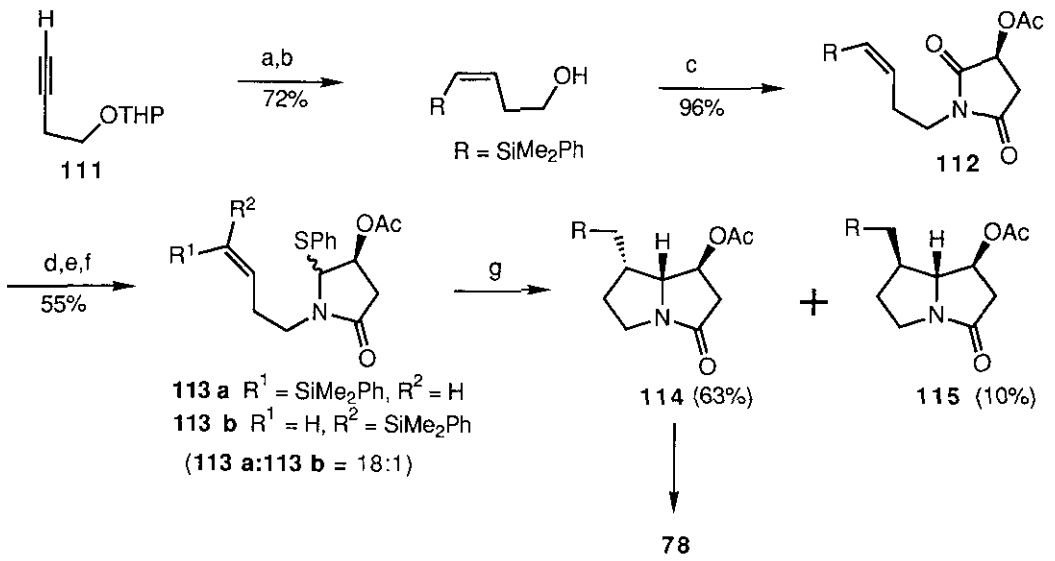
Scheme XXII [a]



[a] (a) CH_2=C=$CHCH_2OH$, EtO_2CNNCO_2Et, Ph_3P, THF; (b) $NaBH_4$, MeOH; (c) Ac_2O,DMAP, CH_2Cl_2; (d) PhSeH, TsOH; (e) *n*-Bu_3SnH, AIBN, PhH, Δ; (f)SeO_2, AcOH; (g) $LiAlH_4$.

Vinylsilanes as addends for free radical cyclization have been examined (Scheme XXIII).[31] The precursor 113 (cis:trans = 18:1) was treated under such reaction conditions as mentioned above for the selenide 109 to afford the pyrrolizidinones 114 and 115 in 63% and 10% yields, respectively. A mixture of isomeric indolizidinones (18%) and a reduction product (3%) were also isolated. A

Scheme XXIII[a]



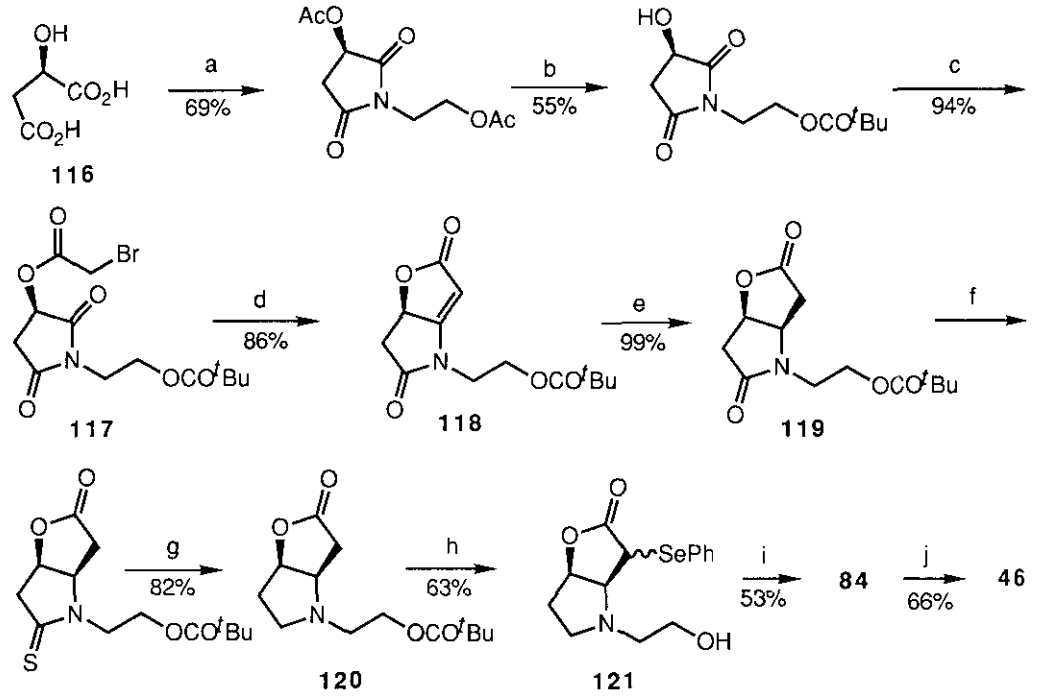
[a] (a) *n*-BuLi; $PhMe_2SiCl$; (b) Cy_2BH-THF; HOAc, Δ; TsOH, MeOH; (c) Ph_3P, **100**, EtO_2CNNCO_2Et, THF; (d) $NaBH_4$, MeOH; (e) Ac_2O, DMAP, CH_2Cl_2; (f) TsOH, PhSH; (g) *n*-Bu_3SnH, AIBN, PhH, Δ.

1.3:1 mixture of the cis and trans olefinic compounds 113 also gave nearly the same results of the free radical cyclization. This finding suggested that an isomerization of cis olefin to the trans isomer took place prior to cyclization. The major product 114 was converted to (-)-dihydroxyheliotridane 78.

An enantioselective synthesis of (+)-retronecine 46 from (*R*)-malic acid 116 has been published by Yamada's group.[32] A key step for the C(1)-C(8) bond formation was achieved by utilizing a novel intramolecular Wittig reaction[33] of the imide 117 prepared from (*R*)-malic acid 116 (Scheme XXIV). Catalytic hydrogenation of the conjugated lactone 118 gave the cis-fused lactone lactam 119. The selective reduction of the lactam carbonyl group in 119 was successful by using a modified Raucher's procedure.[34] Finally, the conversion of 120 to the tricyclic lactone 84 via the phenylselenyl intermediate 121 avoided the problem encountered in Chamberlin's retronecine synthesis[26] (see Scheme XV). According to the present route, (+)-retronecine 46 was prepared in 5.5% overall yield from (*R*)-malic acid in about 20 steps. The Geissman-Waiss lactone derivative 40 was also synthesized by Yamada's group[35] in 62% yield from (*R*)-malic acid (Scheme XXV).

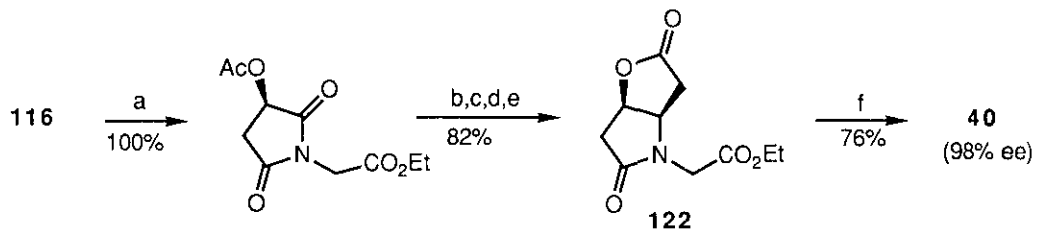
An enantioselective route to (+)-Geissman-Waiss lactone 39 starting from (*S*)-malic acid 74 has been reported.[36] The key step was an intramolecular Michael addition reaction with 1,2-asymmetric induction.[37] A chiral Michael acceptor 126 was prepared from (*S*)-malic acid 74 as a 2:1 mixture of *Z* and *E* isomers (Scheme XXVI). The intramolecular Michael addition reaction proceeded under the optimum conditions examined to give, after cleavage of the MOMO ether, a separable mixture of the cis bicyclic lactone 127 and the trans hydroxy ester 128 (1:7.8). The preference for the formation of the 2(*R*)-isomer 128 in the cyclization was

Scheme XXIV [a]



[a] (a)AcCl; $HOCH_2CH_2NH_2$; AcCl; (b) dry HCl-EtOH; pivaloyl chloride/Py; (c) $BrCH_2COBr$(1.2 eq.), Py (1.5 eq.); (d) Ph_3P, MeCN; Et_3N; (e) H_2, 5% Rh/Al_2O_3, EtOAc; (f) Lawesson's reagent; (g) $Et_3O^+ BF_4^-$, CH_2Cl_2; $NaBH_3CN$, MeOH; (h) LDA, PhSeCl; 6 *N* -HCl; (i) *n* -BuLi; TsCl; LDA-HMPA; (j) $LiAlH_4$; 30% H_2O_2, AcOH.

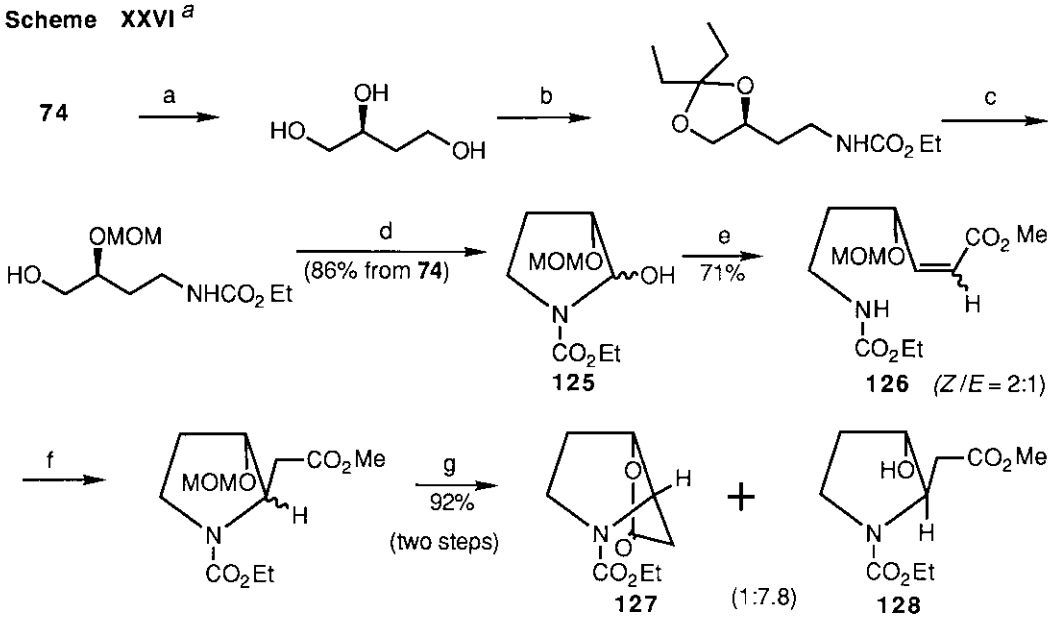
Scheme XXV[a]



[a] (a) AcCl; $NH_2CH_2CO_2Et$; AcCl; (b) AcCl-EtOH; (c) $BrCH_2CO_2Br$ (1.1 eq.), Py (1.2 eq.); (d) Ph_3P, MeCN; Et_3N; (e) H_2, 5% Rh/Al_2O_3; (f) Lawesson's reagent, PhMe; $EtO_3^+BF_4^-$, CH_2Cl_2; $NaBH_3CN$, MeOH-AcOH (92:8).

rationalized by consideration of the transition state 123 in Figure 2. Because of the high degree of steric and electronic repulsion between the ester group and the MOMO function in the transition state 124, Michael addition reaction of the Z-olefinic isomer should preferentially afford the 2(*R*)-isomer 128. This was proved to be the case when the pure Z-olefinic isomer 126, prepared by a modified Still's method,[38] was treated under the Michael reaction conditions followed by claevage of the MOMO ether to result in very highly selective formation of

Scheme XXVI [a]



[a] (a) $B(OMe)_3$, $BH_3{\cdot}SMe_2$, MeOH; (b) $Et_2C(OMe)_2$, TsOH; phthalimide, Ph_3P, EtO_2CNNCO_2Et; $NH_2NH_2{\cdot}H_2O$, EtOH; $ClCO_2Et$, Et_3N; (c) 6 *N* HCl, THF; TBDMSCl, imidazole, DMAP; $ClCH_2OMe$, *i*-Pr_2NEt; *n*-Bu_4NF; (d) $(COCl)_2$, DMSO, Et_3N; (e) $(MeO)_2POCH_2CO_2Me$, $KN(TMS)_2$, 18-crown-6, THF, 3.5 h; (f) KH, 18-crown-6, DME, 0 °C, 21 min; (g) EtSH, $BF_3{\cdot}OEt_2$.

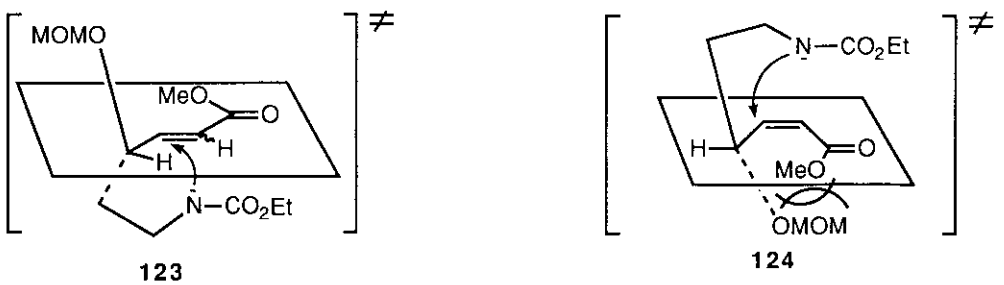
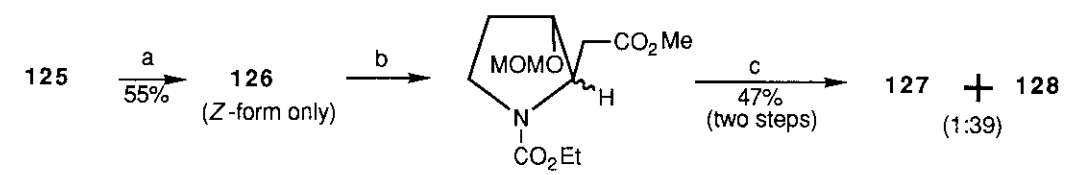


Figure 2

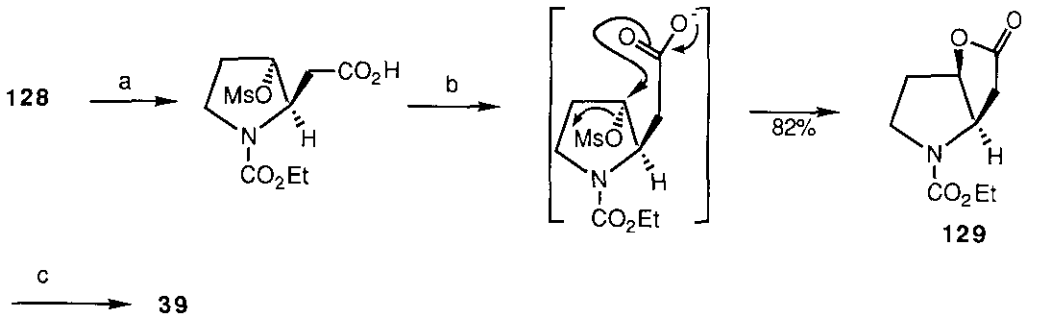
Scheme XXVII [a]



[a] (a) $(CF_3CH_2O)_2POCH_2CO_2Me$, KH, DME, 3 h; (b) KH, 18-crown-6, DME, 0 °C, 9 min; (c) EtSH, $BF_3{\cdot}OEt_2$.

the 2(*R*)-isomer 128 (127:128 = 1:39) (Scheme XXVII). The hydroxy group in 128 was inversed to form the cis-fused bicyclic lactone 129 which was converted to (+)-Geissman-Waiss lactone 39 according to the method of Geissman and Waiss[3] (Scheme XXVIII). Another similar synthesis of (+)-Geissman-Waiss lactone from *L*-(+)-diethyl tartrate was also discussed.[36]

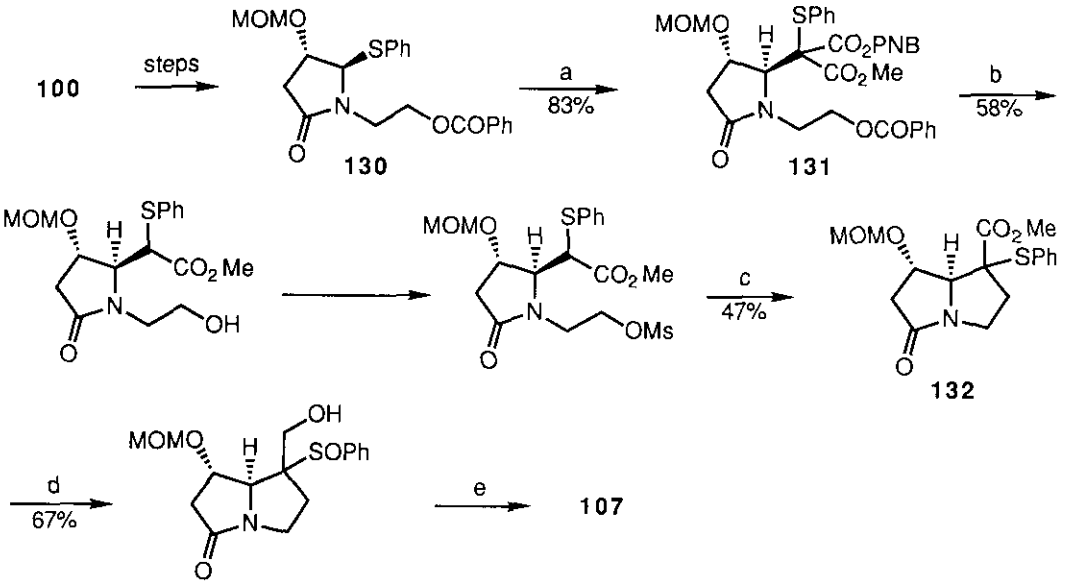
Scheme XXVIII[a]



[a] (a) $MeSO_2Cl$, Et_3N, DMAP; LiOH, dioxane, H_2O; (b) K_2CO_3, 18-crown-6 (cat), MeCN; (c) $Ba(OH)_2 \cdot 8H_2O$, then HCl.

An intermolecular carbenoid displacement reaction has appeared in the stereoselective synthesis of (+)-heliotridine and (+)-retronecine.[39] The sulfide compound 130 was obtained in five steps from the chiral imide 100 previously prepared by Chamberline and Chung[26a] from (*S*)-malic acid. The intermolecular carbenoid displacement reaction of 130 was done with methyl p-nitrobenzyl α-diazo-

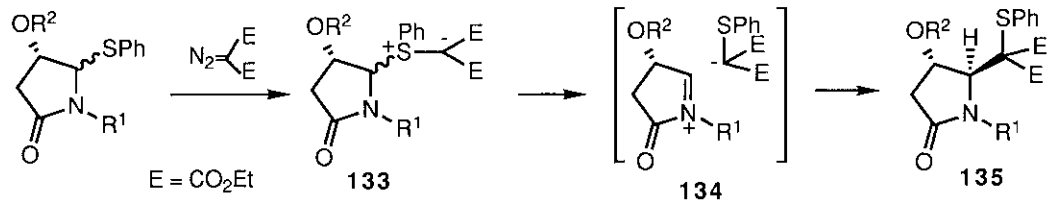
Scheme XXIX[a]



[a] (a) $MeO_2CC(N_2)CO_2PNB$, $Rh_2(OAc)_4$ (cat), PhH, reflux; (b) H_2, Pd/C, MeOH; (c) I^-; $LiN(TMS)_2$, THF, -78 to 0 °C; (d) $LiAlH_4$, Et_2O, 0 °C; MCPBA; (e) PhMe, reflux; HCl, MeOH; Ac_2O/Et_3N, CH_2Cl_2.

malonate in refluxing benzene in the presence of a catalytic amount of rhodium acetate to give the product 131 in 83% yield (Scheme XXIX). This reaction is accounted as illustrated in Scheme XXX. The chiral acetoxy group in the acyliminium ion 134 generated from the ylide 133 blocked well the α-face of C=N double bond; the resultant predominant attack of the anion from the β-face gave

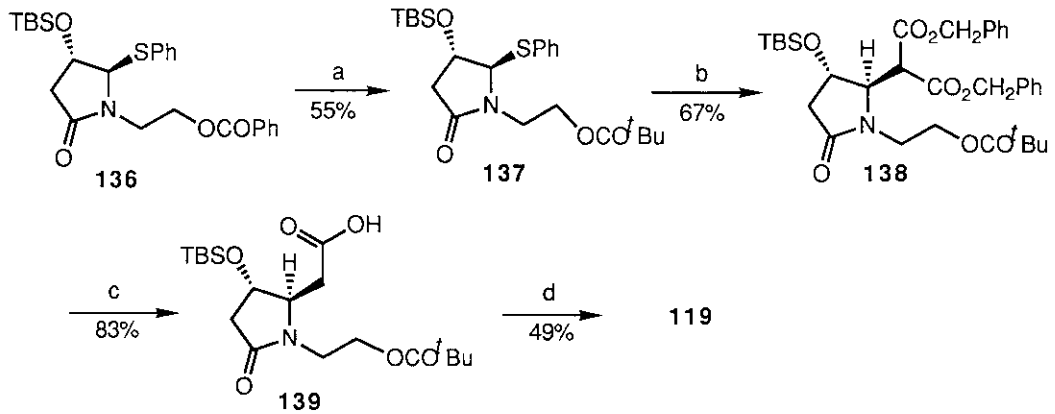
Scheme XXX



the 2,3-trans-pyrrolidinone 135. Compound 131 was then converted to the known intermediate 107 via 132; compound 107 has been shown to be useful for (+)-heliotridine synthesis[28] as described in Scheme XX.

The same strategy[39] has been applied to the synthesis of the known bicyclic compound 119 reported by Yamada's group[32] in the synthesis of (+)-retronecine 46 (see Scheme XXIV). Thus, the sulfide 137 prepared from 136 was subjected to the intermolecular carbenoid displacement reaction to afford, after desulfurization, the product 138 in 67% overall yield. This compound was then transformed to the known 119 via the carboxylic acid 139 under inversion of the stereochemistry at the carbon atom substituted with the oxygen function (Scheme XXXI).

Scheme XXXI[a]



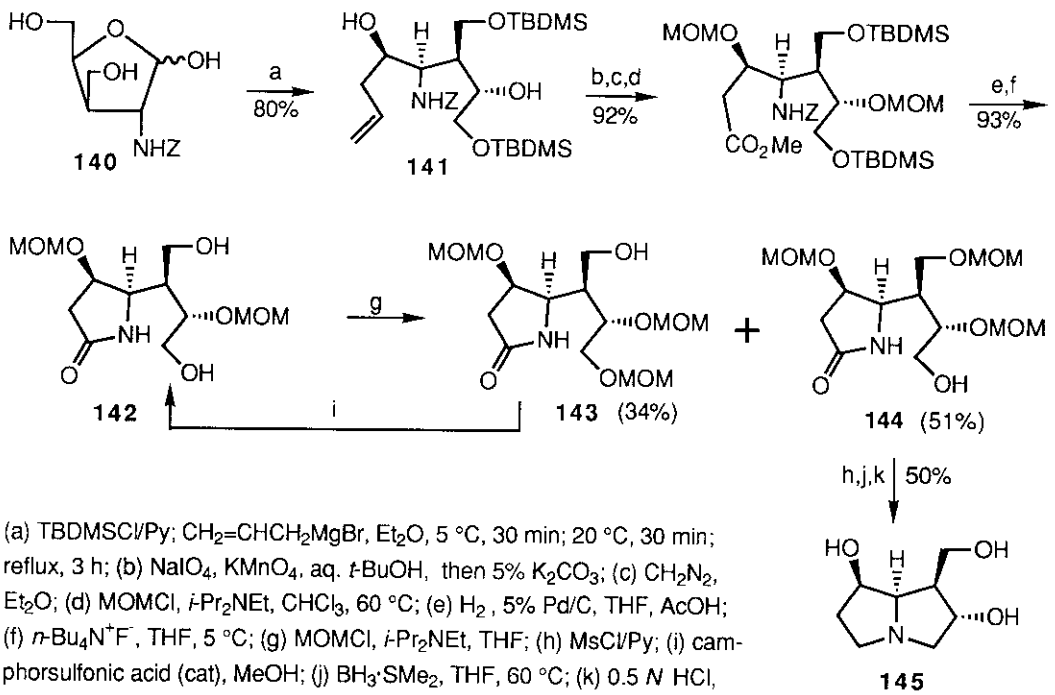
[a] (a) K_2CO_3, MeOH; *t*-BuCOCl/Py, Et_2O; (b) $N_2=C(CO_2CH_2Ph)_2$, $Rh_2(OAc)_4$, PhH, reflux; Raney Ni; (c) H_2, Pd/C, MeOH; PhMe , reflux; (d) *n*-$Bu_4N^+F^-$, THF; EtO_2CNNCO_2Et, Ph_3P, THF.

4. UTILIZATION OF CARBOHYDRATES

The first asymmetric synthesis of (-)-rosmarinecine 145, a pyrrolizidine triol, from a carbohydrate precursor has been reported by Tatsuta's group.[40] An intermediate 140 prepared from methyl α-*D*-glucosaminide[41] was used in the synthe-

sis (Scheme XXXII). Aldol condensation of the di-TBDMS ether of 140 with excess allylmagnesium bromide afforded the single threo amide alcohol 141. The *R* configuration of the newly formed asymmetric carbon atom with a hydroxy group was rationalized by a chelation-controlled approach.[42] Compound 141 was converted to the diol lactam 142 via mainly the oxidation and lactamization procedures. Selective methoxymethylation of the two hydroxy groups in 142 with a little success gave the desired mono-ol 144 in 51% yield accompanied by 143 (34%), which could be used for recycling. Mesylation, reduction, and deprotection of 144 afforded (-)-rosmarinecine 145 (Scheme XXXII).

Scheme XXXII [a]

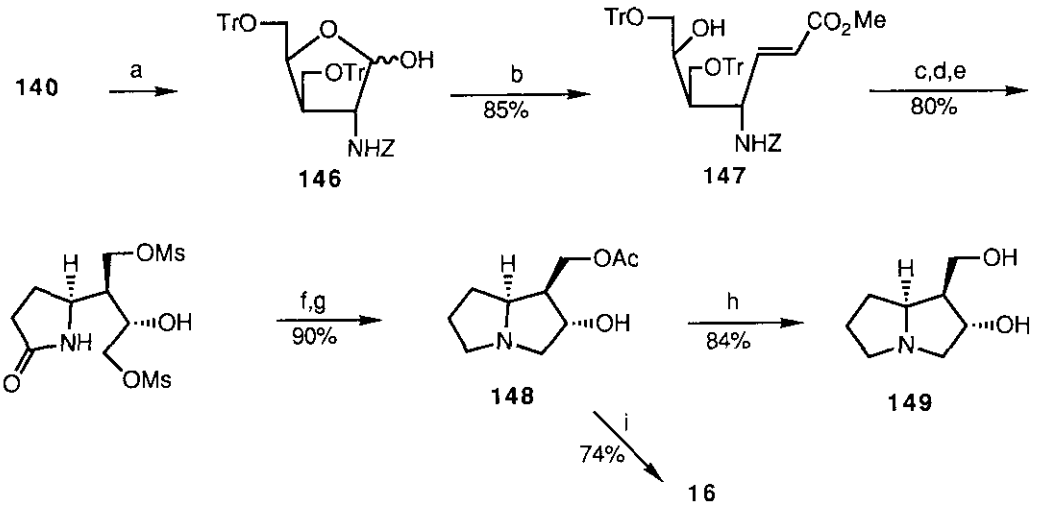


[a] (a) TBDMSCl/Py; CH_2=$CHCH_2MgBr$, Et_2O, 5 °C, 30 min; 20 °C, 30 min; reflux, 3 h; (b) $NaIO_4$, $KMnO_4$, aq. *t*-BuOH, then 5% K_2CO_3; (c) CH_2N_2, Et_2O; (d) MOMCl, *i*-Pr_2NEt, $CHCl_3$, 60 °C; (e) H_2, 5% Pd/C, THF, AcOH; (f) *n*-$Bu_4N^+F^-$, THF, 5 °C; (g) MOMCl, *i*-Pr_2NEt, THF; (h) MsCl/Py; (i) camphorsulfonic acid (cat), MeOH; (j) BH_3·SMe_2, THF, 60 °C; (k) 0.5 *N* HCl, dioxane, 80 °C, 6 h.

The same intermediate 140 was also used for the synthesis of pyrrolizidine di- and mono-ols, namely (-)-7-deoxyrosmarinecine 149 and (-)-isoretronecanol 16 (Scheme XXXIII). Wittig reaction of 146 gave the unsaturated ester 147 which, upon hydrogenation, lactamization, and mesylation, gave a lactam. Its reductive cyclization followed by displacement of the mesylate with acetate anion gave the acetate 148, which was deacetylated to form (-)-7-deoxyrosmarinecine 149. The conversion of the acetate 148 to (-)-isoretronecanol 16 was accomplished by the known procedure[43] shown in Scheme XXXIII.

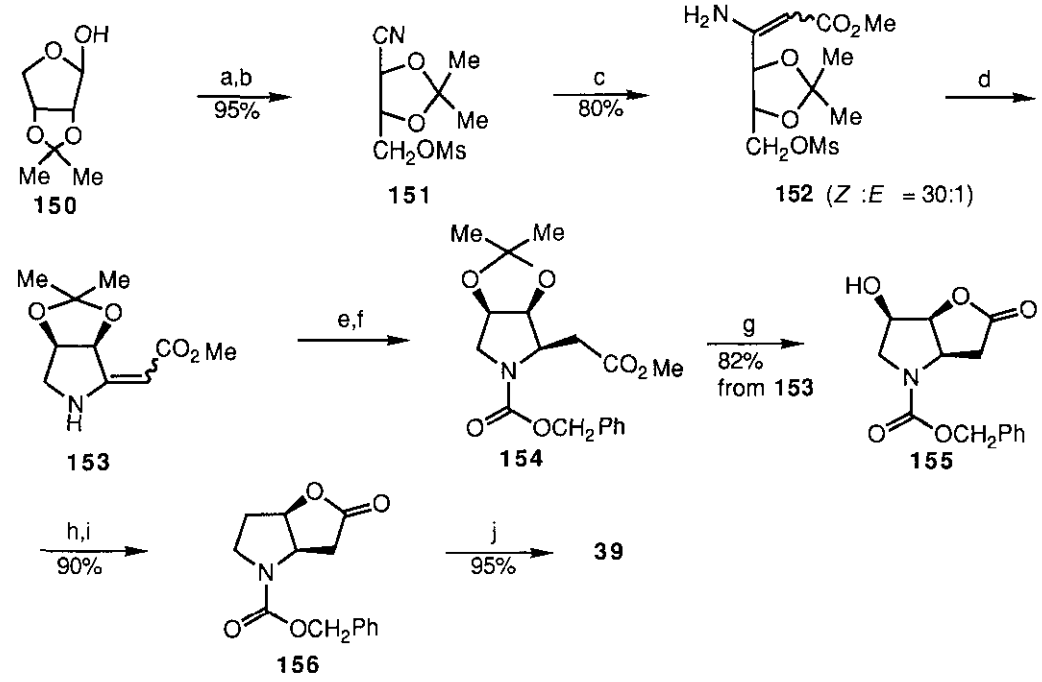
A synthesis of optically active Geissman-Waiss lactone 39 from a carbohydrate derivative has been published by Buchanan's group.[44] 2,3-*O*-Isopropylidene-*D*-erythrose 150[45] was converted, via the corresponding oxime, into the cyanomethanesulfonate 151, which was allowed to react with methyl bromoacetate in the presence of activated zinc dust to yield the enamino esters 152 (*Z*:*E* = 30:1). Each

Scheme XXXIII [a]



[a] (a) trityl chloride/Py, 70 °C; (b) $Ph_3P{=}CHCO_2Me$, PhMe , 60 °C; (c) H_2, 5% Pd/C, THF, AcOH; (d) Amberlyst 15, MeOH, 60 °C; (e) MsCl/Py, 0 °C; (f) $BH_3{\cdot}SMe_2$, THF, 60 °C; (g) KOAc, DMSO, 80 °C; (h) NH_3, MeOH; (i) $SOCl_2$, reflux; H_2, Raney Ni, EtOH; NH_3, MeOH.

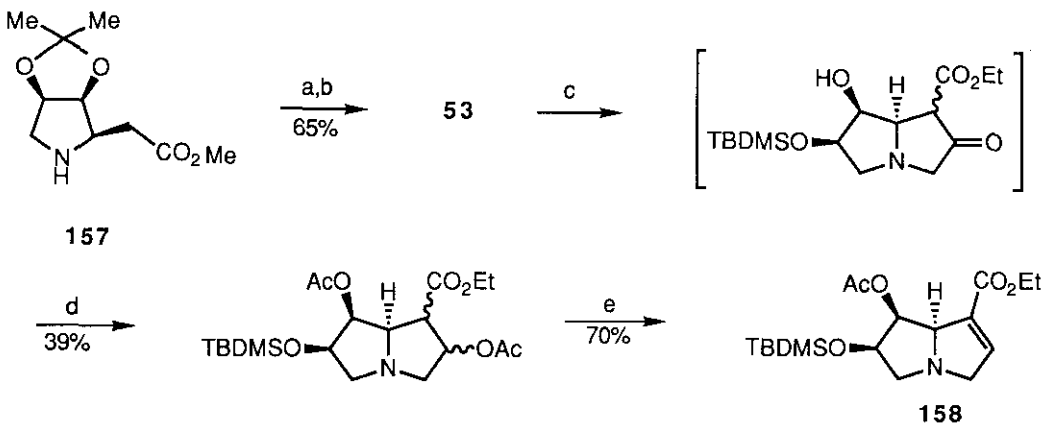
Scheme XXXIV [a]



[a] (a) $NH_2OH{\cdot}HCl$ (10 eq.), Py, rt; (b) $MeSO_2Cl$ (12 eq.), Py, -23 °C; (c) activated Zn, $BrCH_2CO_2Me$ (5 eq.), THF, reflux; (d) DBU (3 eq.), CH_2Cl_2, rt; (e) $NaBH_3CN$, MeOH, HCl; (f) $PhCH_2OCOCl$, Et_3N, CH_2Cl_2; (g) 80% CF_3CO_2H, rt; (h) 1',1-thiocarbonyldiimidazole, Py, THF, reflux; (i) *n*-Bu_3SnH (2.2 eq.), PhH, reflux; (j) H_2, 10% Pd/C, EtOH, HCl.

isomer of the enamino esters 152, upon cyclization in the presence of DBU, reduction with sodium cyanoborohydride, and treatment with benzyl chloroformate, gave the same product 154. Hydrolysis of the isopropylidene group in 154 formed the hydroxy lactone 155 which, after Barton-type deoxygenation,[46] yielded the lactone 156. Hydrogenolysis of the lactone 156 gave the Geissman-Waiss lactone 39 as its crystalline hydrochloride (Scheme XXXIV). The compound 157 obtained from hydrogenation of 153 was converted to the known intermediate 53 previously prepared from (-)-4-hydroxy-*L*-proline by Benn and co-workers[13c] (see Scheme IX). Compound 53 was converted into the possible intermediate 158 for the synthesis of (+)-crotanecine 54[44] (Scheme XXXV).

Scheme XXXV [a]



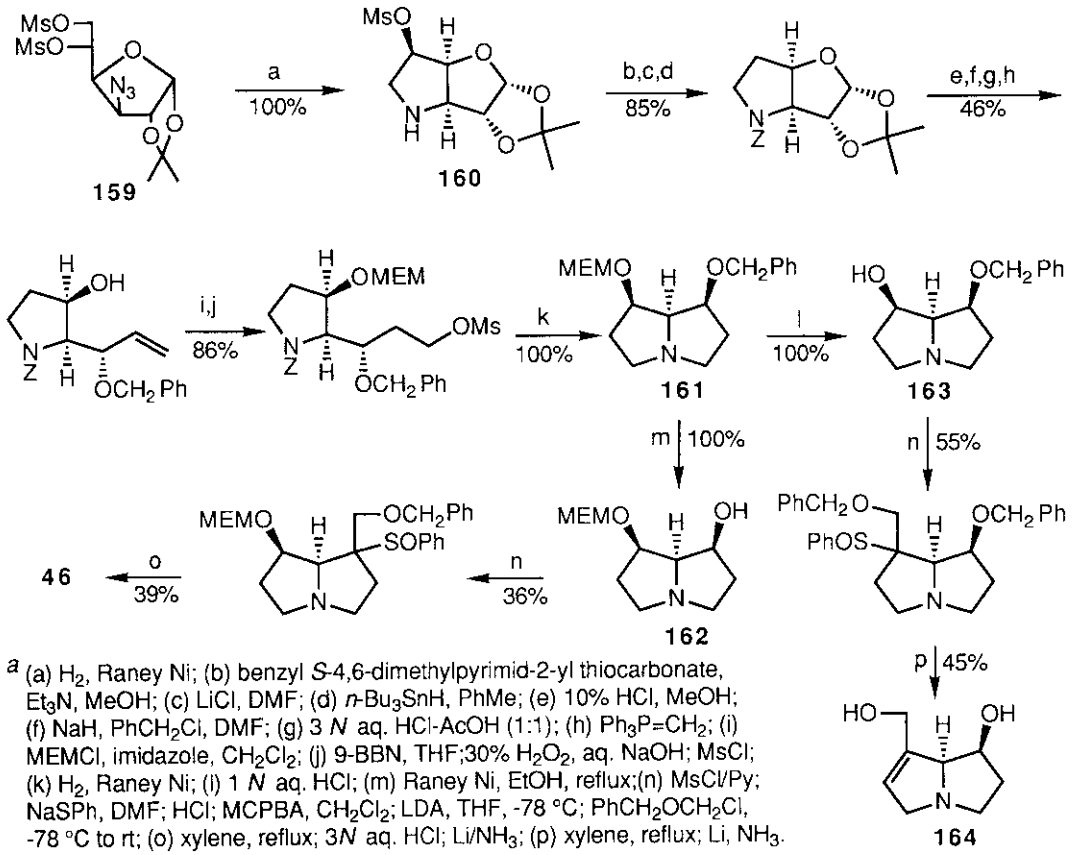
[a] (a) $BrCH_2CO_2Et$, Et_3N, THF; (b) 80% aq. CF_3CO_2H, rt; TBDMSCl, imidazole, DMF; (c) KOEt-PhH, rt, then HOAc; (d) $NaBH_4$, EtOH, then Ac_2O/Py; (e) DBU, CH_2Cl_2, rt.

More recently, a *D*-glucose derivative was utilized by Nishimura's group in the enantioselective synthesis of retronecine and its enantiomer.[47] 3-Azido-1,2-*O*-isopropylidene-5,6-di-*O*-mesyl-α-*D*-glucofuranose 159 obtained from 3-azido-3-deoxy-1,2-O-isopropylidene-α-*D*-glucopyranose[48] on cyclization under the catalytic reduction conditions over Raney nickel gave the product 160. Deoxygenation and homologation of the side chain gave 161, a pyrrolizidine diol protected by different groups. The differentiation of the two hydroxy groups on C(1) and C(7) was accomplished by selective removal of each protecting group to give 162 and 163, respectively. Homologation of 162 and 163 on the carbons in which the free hydroxy groups were located yielded (+)-retronecine 46 and its enantiomer 164, respectively (Scheme XXXVI). No significant difference in the cytotoxicity between these two compounds was found.

5. UTILIZATION OF CHIRAL AUXILIARIES

The first example using a chiral auxiliary in an asymmetric cyclization process to form (+)-trachelanthamidine 9 was reported by Takano's group.[49] Deaminative coupling of 4-aminobutyral dimethyl acetal 165 with freshly prepared

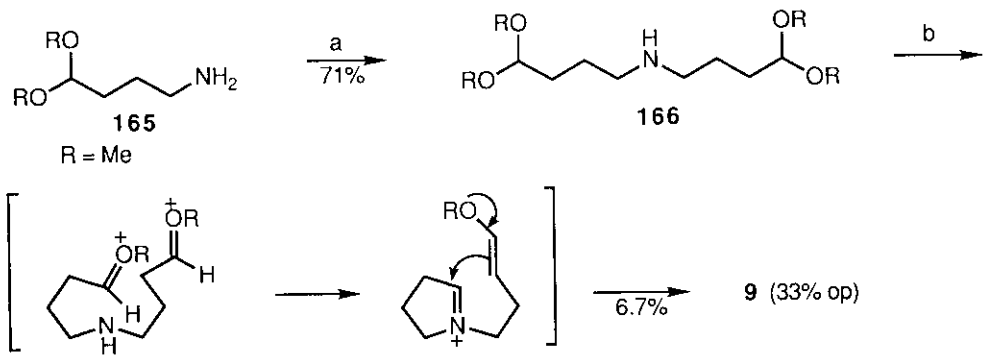
Scheme XXXVI [a]



[a] (a) H_2, Raney Ni; (b) benzyl *S*-4,6-dimethylpyrimid-2-yl thiocarbonate, Et_3N, MeOH; (c) LiCl, DMF; (d) *n*-Bu_3SnH, PhMe; (e) 10% HCl, MeOH; (f) NaH, $PhCH_2Cl$, DMF; (g) 3 *N* aq. HCl-AcOH (1:1); (h) $Ph_3P{=}CH_2$; (i) MEMCl, imidazole, CH_2Cl_2; (j) 9-BBN, THF;30% H_2O_2, aq. NaOH; MsCl; (k) H_2, Raney Ni; (l) 1 *N* aq. HCl; (m) Raney Ni, EtOH, reflux;(n) MsCl/Py; NaSPh, DMF; HCl; MCPBA, CH_2Cl_2; LDA, THF, -78 °C; $PhCH_2OCH_2Cl$, -78 °C to rt; (o) xylene, reflux; 3*N* aq. HCl; Li/NH_3; (p) xylene, reflux; Li, NH_3.

Raney nickel catalyst (W-2) gave the symmetric aminodiacetal 166, which, upon treatment with pyridinium *D*-camphor-10-sulfonate in aqueous media at 100°C followed by reduction with sodium borohydride, afforded (+)-trachelanthamidine 9 in 6.7% yield and in 33% optical purity (Scheme XXXVII).

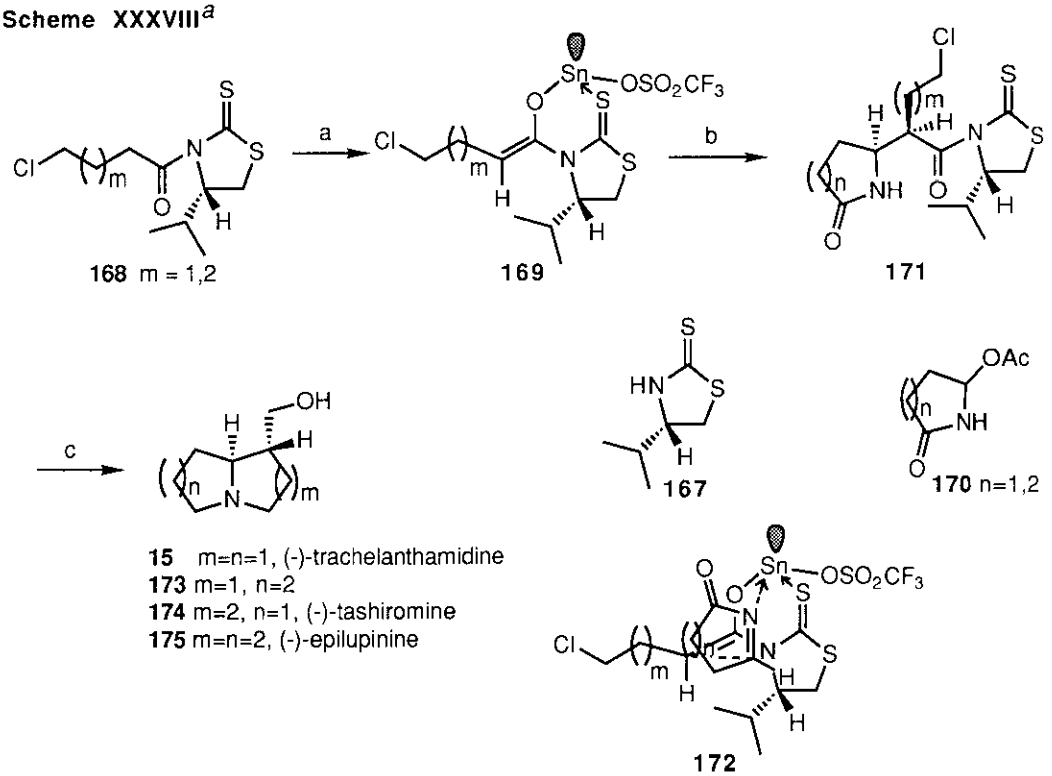
Scheme XXXVII [a]



[a] (a) Raney Ni, PhH, reflux; (b) pyridinium *D*-camphor-10-sulfonate, H_2O, 100 °C; $NaBH_4$.

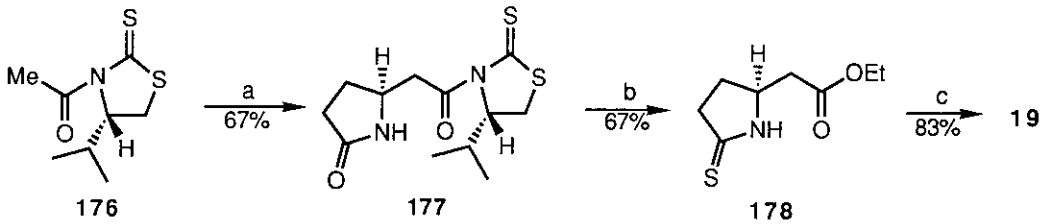
The authors' group has demonstrated that a chiral heterocyclic compound, 4(*S*)-isopropyl-1,3-thiazolidine-2-thione (4(*S*)-IPTT) 167 served as an excellent chiral auxiliary in various cases of chiral recognition.[50] Among them, alkylations of the chiral tin(II) enolates derived from 3-acyl-4(*S*)-IPTT with 4-acetoxy-2-azetidinones[50a,b,f] and α,β-unsaturated aldehydes[50c] have given interesting results, particularly for β-lactam synthesis. This procedure has been expanded to the field of alkaloid synthesis. An extremely short chiral synthesis of (-)-trachelanthamidine 15 was reported[51] which consisted of a highly diastereoselective alkylation of chiral tin(II) enolates onto cyclic acylimines followed by reductive annulation of the resultant alkylation products (Scheme XXXVIII). 3-(ω-Chloroacyl)-4-(*S*)-isopropyl-1,3-thiazolidine-2-thiones 168 (m = 1, 2) were treated with tin(II) trifluoromethanesulfonate and *N*-ethylpiperidine in THF to form the tin(II) enolates 169 (m = 1, 2), which reacted with 5-acetoxy-2-pyrrolidinone 170 (n = 1) or 6-acetoxy-2-piperidinone 170 (n = 2) to yield the alkylation products 171 in 57-73% yields and with ≥93-≥97% diastereomeric excess. The high diastereoselectivity of this alkylation reaction was rationalized by a chelation-controlled process via the transition state 172. Conversion of 171 (m = n = 1) to (-)-trachelanthamidine 15 was achieved by one reagent ($LiAlH_4$) and one pot process in 44% chemical yield and in ≥99% optical purity. Similarly, two indolizidine-type compounds 173 and 174[52] and (-)-epilupinine 175 were synthesized. Use of 4(*R*)-enantiomer instead of 4(*S*)-IPTT provides a synthetic route to

Scheme XXXVIII[a]



[a] (a) $Sn(OSO_2CF_3)_2$, *N*-ethylpiperidine, THF, -5 to 0 °C, 3-4 h; (b) **170**, THF, -5 to 0 °C, 2 h; (c) $LiAlH_4$, THF, 0 °C, 5 min, then reflux, 2 h.

Scheme XXXIX[a]

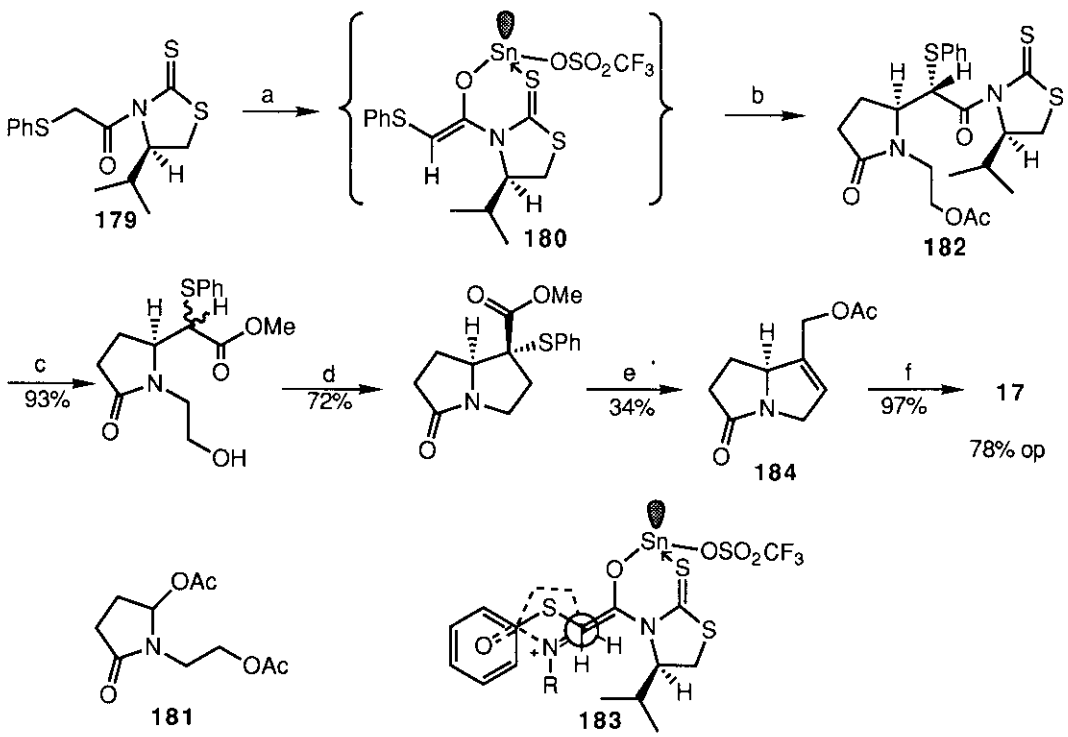


[a] (a) $Sn(OSO_2CF_3)_2$, *N*-ethylpiperidine, THF, -50 to -40 °C, 3 h; **170** (n=1), THF, -5 to 0 °C, 2 h; (b) K_2CO_3, EtOH, rt, 12 h; Lawesson's reagent, PhMe, 105 °C, 1 h; (c) $Et_3O^+BF_4^-$, CH_2Cl_2, rt, 3 h; $NaBH_3CN$, MeOH-AcOH (92:8), rt, 3 h; $BrCH_2CO_2Et$, EtOH, Na_2CO_3, rt, 20.5 h.

both (+)-trachelanthamidine 9 and (+)-epilupinine.

The chiral diester 19 prepared by Rüeger and Benn[9] from *L*-proline has also been efficiently synthesized[53] from the alkylation product 177 which was obtained from 3-acetyl-4(*S*)-IPTT 176 in 67% chemical yield and in 94% diastereomer excess (Scheme XXXIX). Ethanolysis of 177 followed by treatment of the resultant ester with Lawesson's reagent afforded compound 178. Reductive removal of the

Scheme XL[a]

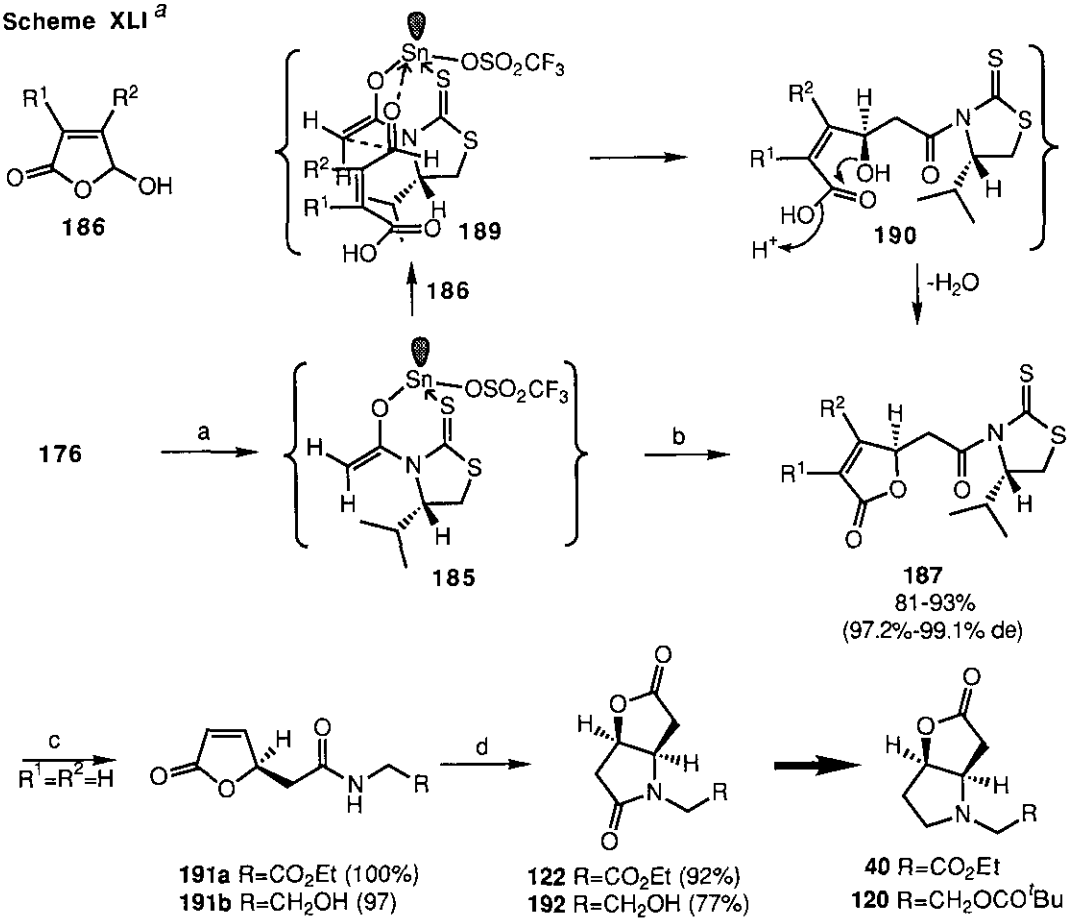


[a] (a) $Sn(OSO_2CF_3)_2$, *N*-ethylpiperidine, THF, -78 °C, 30 min; (b) **181**, THF, -5 to 0 °C, 2 h; (c) 10% KOH-MeOH, rt, 30 min; CH_2N_2; (d) MsCl/Et_3N, THF, rt, 3 h; NaI, THF, rt, 12 h; LDA (1.1 eq.), -78 °C, 2 h, then -30 °C, 3 h; (e) $LiAlH_4$, THF, 0 °C, 30 min; MCPBA, CH_2Cl_2, -78 °C, 30 min; PhMe, reflux, 22 h; Ac_2O/Et_3N, DMAP (cat), CH_2Cl_2, rt, 30 min; (f) $LiAlH_4$, THF, reflux, 80 min.

thiocarbonyl group in 178 and *N*-alkylation of the resultant amine with bromoacetate furnished the chiral diester 19, an intermediate useful for 8α-pyrrolizidine alkaloid synthesis (see Schemes IV, V, and VI). Use of the enantiomer of 177 may provide a useful synthetic route to 8β-pyrrolizidine alkaloids.

An intermolecular asymmetric amidoalkylation reaction employing the chiral tin(II) enolates and achiral acyliminium ions has been achieved and applied to the synthesis of (-)-supinidine 17 (Scheme XL).[54] Contrary to the reaction of the chiral tin(II) enolates with the cyclic acylimines, alkylation of chiral tin(II) enolate 180 onto the acyliminium ion derived *in situ* from the diacetate 181 afforded four diastereomers in a ratio of 82.6 : 7.5 : 6.9 : 3.0. This finding suggested that the reaction of tin(II) enolate 180 with 181 should be fall into a non-chelation control process. Such a transition state is given as 183 in which the π-π attraction between the electron-deficient carbonyl group of the acyliminium ion moiety and the electron-rich phenyl group of the chiral enolate is accounted as one of the factors for the diastereoselectivity. The major product 182 was isolated in 58% yield as a 91 : 9 inseparable mixture of 182 and

Scheme XLI [a]



[a] (a) $Sn(OSO_3CF_3)_2$, *N*-ethylpiperidine, THF, -50 to -40 °C, 3 h; (b) **186**, -5 to 0 °C, 2 h; 5% HCl; (c) NH_2CH_2R, THF, rt, 10 min; (d) NaH, DMF, 10 °C, 5 h; AcOH, -50 °C.

one of the other three minor diastereomers. The alkylation product 182 was then converted to the unsaturated pyrrolizidinone 184 via intramolecular annulation and manipulation of the sulfur group to introduce a double bond at the C(1)-C(2) position. Reduction of 184 gave (-)-supinidine 17 in 97% yield and in 78% optical purity (Scheme XL).

Efficient utilization of the chiral tin(II) enolate appears in a very recent work of γ-alkylated butenolide synthesis[55] (Scheme XLI). This new general synthetic method is basically developed from the asymmetric aldol reaction reported by us,[50c] but in the present case, the masked 1,4-cis-unsaturated aldehydic acids (as 5-hydroxy-2(5*H*)-furanones 186) are employed to allow further lactonization of the resultant chiral γ-hydroxy-α,β-unsaturated carboxylic acids 190. The aldol reaction and lactonization can take place in a one-pot manner with very high diastereoselectivities, and the chiral butenolides are formed in excellent chemical yields. Compounds 187 could be considered as versatile chiral precursors for natural product synthesis. This is exemplified by the expeditious synthesis of chiral Geissman-Waiss lactones useful for (+)-retronecine synthesis (Scheme XLI). Aminolysis of 187 (R^1 = R^2 = H) followed by intramolecular Michael addition of the amide anions formed from 191 furnished the bicyclic compounds 122 and 192 in excellent yields. These compounds were then convertred to the known Geissman-Waiss lactone derivatives 40 and 120, which were previously prepared from (-)-4-hydroxy-*L*-proline[13b] and (*R*)-malic acid,[32,35] respectively (see Schemes VIII, XXIV and XXV).

6. CONCLUSION

A number of asymmetric syntheses of pyrrolizidine alkaloids have been successfully performed by utilizing chiral synthons derived from naturally occurring substances. The elaborate synthetic methods based on the efficient asymmetric induction without the direct use of natural products have also been disclosed. The versatile asymmetric pyrrolizidine syntheses which involve the novel design will be extensively developed and will be expected to promise discovery of new drugs.

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